Studies on Some Synthetic Aspects of Pyridinium and Sulphonium Ylides

A

THESIS

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by

Ajay Kumar Gupta
M.Sc.

Under the supervision of

Dr. Manoj Kumar Gupta

Professor & Head

Deptt. of Applied Sc. & Humanities

BUNDELKHAND INSTITUTE OF ENGINEERING AND TECHNOLOGY

Jhansi (U.P.)

Dedicated

to

my

parents

Dr. K.C. Gupta

&

Smt. Sudha Gupta

CONTENTS

Certificate

Certified that the thesis entitled "Studies on some synthetic aspects of pyridinium and sulphonium ylides by Mr. Ajay Kumar Gupta emodies the work carried out by him under my supervision. This work reported in thesis in all original and has not been submitted elsewhere for the award of a degree. Mr. Ajay kumar Gupta has worked for more than 200 days attendance in the laboratory during this work.

Place : Jhansi

Date :18·6·08

(Dr. Manoj Kumar Gupta)
Profession & Head
Department of Applied Science & Humanities
B.I.E.T., Jhansi

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Ajay Kumar Gupta

Place : Jhansi (Ajay Kumar Gupta)

Date : 18-6-08

Preface

The thesis entitled ***"Studies on synthetic aspects of pyridinium and sulphonium ylides"*** has been divided in to eight chapters and each chapter describes specific aspects of ylide chemistry.

In Chapter I, an exhausting literature survey on preparation and a reactions leading to the synthesis of cyclic and heterocyclic compounds using stablized and non stabilized pyridinium and sulphonium ylides, have been reported.

Chapter II decribes the detailed studies on the reactions of some carbonyl stabiliyed pyridinium ylides (Azomethine ylides) generated ***in situ*** from 3-chlorophenacylpyridinium bromide, 3-methylphenacylpridinium bromide, 3-methoxyphenacyl pyridnium bromide and 3-ethoxyphenacylpridinium bromide with α,β-unsaturated carbonyl compunds have been reported.

In Chapter III, deals with the reactivity of β-picolinium ylides and γ-picolinium ylides towards a variety of α,β-unsaturated ketones to afford some new 2,4,6-triarylsubstitutedpyridines.

In Chapter IV, froms the subject matter of author's investigation, on the synthesis of 2,4,6-triarylsubstituted pyridines via phenacylide-neisoquinolinium ylides and 4-phenylphenacylideneisoquinolinium ylides generated ***'in situ'*** from their respective quaternary salts.

In Chapter V, exploration of studies is directed towards the

reactivity of o-nitrobenzylidenepyridinium ylide generated *'in situ'* from o-ntirobenzylpyridinium bromide with a large variety of α,β-unsaturated ketones in presence of sodium acetate and anhydrous $ZnCl_2$ or $AlCl_3$ at reflux temperature to give 1,3-diaryl-5-nitro naphthalenes in 45-75% yield.

In Chapter VI, we have concentrated our studies on synthesis of some new 2,4,6-trisubstitutedphenylpyrimidines using 4-nitro and 4-fluorophenacyldimethylsulfonium bromides with aromatic aldehydes.

In Chapter VII, Synthesis of 1,3,5-triaylsubstitutednaphthalene using non stablized π-sulfurance (sulphonium ylides) have been reported. The Reaction of o-substitutedbenzyldimethylsulfonium bromides with α,β-unsaturatedketones in presence of anhydrous $ZnCl_2$ or $ArCl_3$ at reflux temperature to give 1,3-diaryl-5-substituted naphthalenes have been reported.

In Chapter VIII is the result of authors investigations on the reactivity of some sulphonium & pridinium ylides with aromatic amines in presence of dimethylaniline to efford 2-arylindoles introduce. The reaction these ylides with 1 & 2 napthu; amines to afford new substituted benzinzoles. The course of reaction proceeded via the nucleophilic addition of aromatic amines to carbonyl group of pyridinium & sulfonium salts which, in tern, underwent ylide formation after dehydohalogenation. These ylides elimination of Me_2S underwent H^+ shift to form 2-arylindole darivatives.

Chapter-I

Chapter -I

STUDIES ON SOME SYNTEHTIC ASPECTS OF PYRIDINIUM AND SULPHONIUM YLIDES

INTRODUCTION

I.A. Pyridinium Ylides (Cycloimmonium ylides)

Ylides (1) are zwitterionic compounds in which an anion is covalently bonded to a positively charged heteroatom and are considered as resonance hybrid of two limiting structures viz. the ylide form (1a) and the ylene form (1b). One of these, the ylide form (1a) emphasizes the dipolar zwitterionic nature involving an onium centre at element like nitrogen, phosphorus or arsenic, next to a carbanionic function, which may atleast partially be delocalized into suitable substituents. On the other hand, in the ylene form (1b), a true double bond is postulated between the onium centre and the ylidic carbon, thus reducing or even eliminating the formal charges at these atoms.[1,2]

The application of modern physical techniques and the results of sophisticated theoretical calculations[3-5] have made increasingly clear that the ylide form predominates in the ground state. Most of the

early investigations successfully used in this description for most of their problems of structures, reactivity and for the rationalization of reaction mechanism.[2-6] Therefore, it is with justification that the term ylide is used now-a-days exclusively in the literature.

The reactivity of these ylides depends both on the properties of the carbanion and the possible involvement of the heteroatom. These compounds vary widely in stability, depending on the symmetry of the molecules and the extent of p_π-d_π bonding. A quantitative comparison of the stability of the ylides formed by different elements have been made using the rates of alkali catalysed exchange[7] of the α-hydrogen atom of the corresponding salts. The acidity of salt and, hence, the stability of the ylide is greatly affected by the change in structure.

Ylides have been classified into two main groups on the basis of stability and the ease with which they undergo reaction with a variety of electrophilic substrates. The first and the larger group comprises the ylides also called "non stabilized ylides" which are generated in the solution from their precursors but could not be isolated due to lack of the stabilizing factors and undergo reactions '***in situ***'. These ylides may further be divided into two categories depending upon the attachment of alkyl or arylalkyl groups with the heteroatom. The arylalkylidene ylides, some time designated as "semi-stabilized ylides" which could not be isolated but persisted in solution for a considerable period in contrast to the alkylidene ylides which

are very short-lived. The second and smaller group consists of "stabilized ylides" and is taken to imply an ylide which may be isolated, purified, usually stored in atmosphere and used in subsequent reactions. The stability of these ylides may be attributed to the attachment of the electron withdrawing groups with the ylidic carbanion.

In recent years, synthetic applications of ylides have been reallized and studies on these reactive intermediates have been expanded in many directions which led to the exploration of the ylides of nitrogen, phosphorus, arsenic and sulphur as evidenced by research monographs[1,2,8-12] and comprehensive review articles.[13-23] The involvement of a particular heteroatom results into marked differences in the chemical and physical behaviour of different types of ylides.

The development of the chemistry of nitrogen ylides began with the early attempts to prepare organic derivatives containing pentavalent nitrogen. for this purpose, Schlenk and Holtz[24] treated tetramethyl ammonium chloride with sodium triphenylmethylide (2) and isolated a red product, soluble in organic solvent, to which they assigned structure (3) (Scheme IA.1).

Later, Hager an Marvel[25] attempted to prepare analogous compounds in which all the five groups around nitrogen were more equivalent. These workers found that the reaction of triethylbenzylammonium bromide with ethyl lithium did not produce tetraethylammonium benzylide thus, ruling out the existence of any

intermediate in which all the five groups bound to the nitrogen approached equivalency. From this observoation, Hager and Marvel[25] concluded that the material prepared by Schlenk and Holtz[24] was tetraalkyl ammonium salt of relatively stable triphenylmethyl carbanion (3) rather than derivative of pentavalent nitrogen.

In 1944, Wittig and Felletshcin[26] began a reinvestigation of the pentavalent nitrogen problem and succeeded in isolating a red powder by the treatment of 9-flourenylidenetrimethylammonium bromide (4) with phenyllithium in ether. However, since benzene isolated products from the reaction mixture, the compound could not be pentavalent nitrogen derivative and was assigned an ylide structure on the basis of its reaction with water, methyl iodide, iodine and benzyl bromide (Scheme IA.2). Following this initial preparation of a stable material having an ylide structure, a variety of nitrogen ylides have been prepared, characterized and their chemistry has been reviewed.

The N-ylide have been classified according to the onium group structure into: ammonium ylides (5), cycloammoniumylides (6), immoniumylides (7), cycloimmoniumylides (8), nitrileylides (9) and diazoniumylides (10). The cycloimmonium-ylides have been further divided into five-membered cycloimmonium-ylides and six membered cycloimmoniumylides which include pyridinium (11) and benzopyridinium ylides (12).

Neglecting the coulombic interaction as a minor contribution to

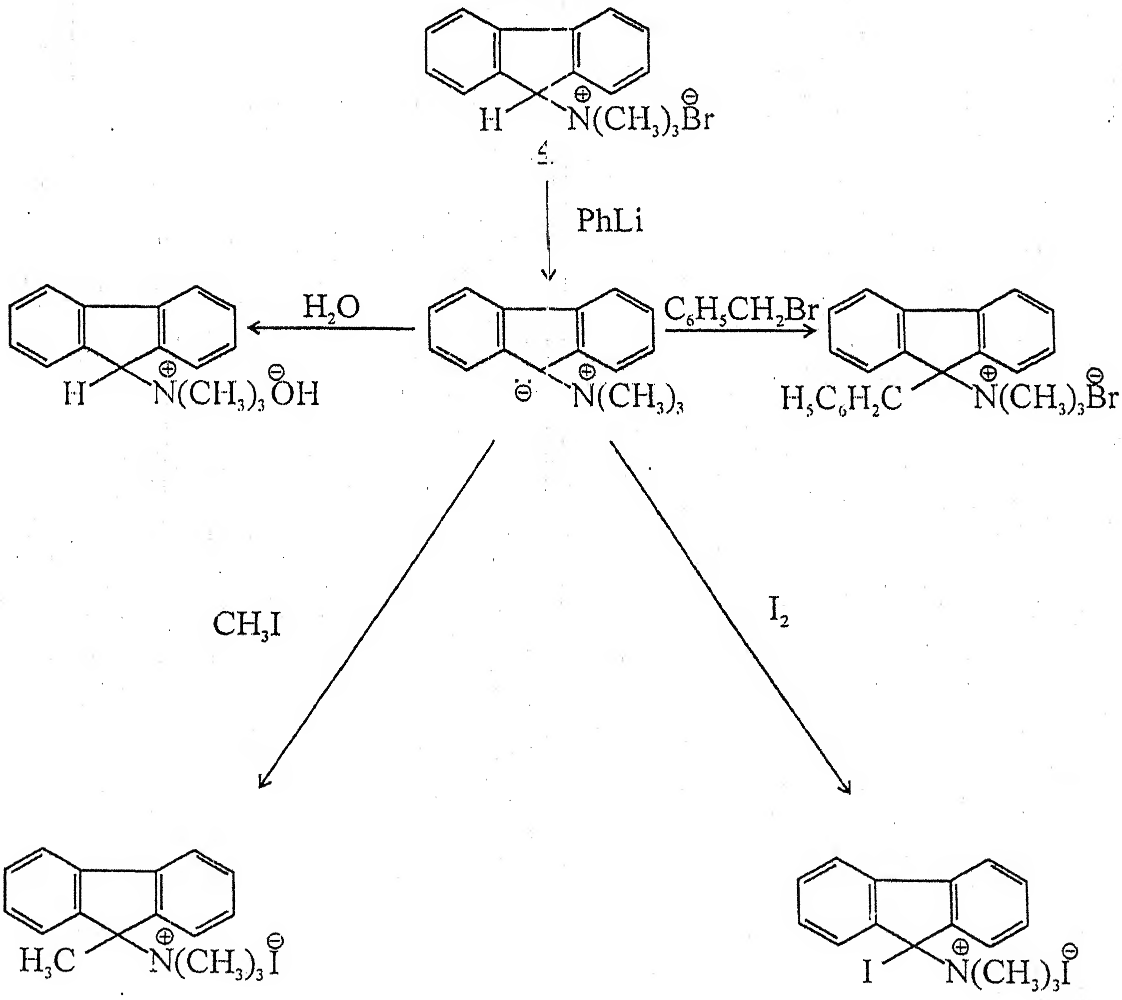
1a **1b**

(where X may be N, P, As, S etc.)

<u>**SCHEME IA.1**</u>

$$\underset{\underline{2}}{(Ph)_3\overset{\ominus}{\ddot{C}}\,\overset{\oplus}{Na} + (CH_3)_4\overset{\oplus}{N}\,.\,\overset{\ominus}{Cl}} \longrightarrow \underset{\underline{3}}{(CH_3)_4\overset{\oplus}{N} - \overset{\ominus}{\ddot{C}}\,(Ph)_3} + NaCl$$

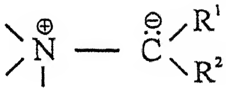
<u>**SCHEME IA.2**</u>



stability, the N-ylide, stability is determined by two important factors: the structure of the onium group and the anionic part. N-ylides due to absence of d-orbital overlap, do not contribute the ylene form and the only stabilizing factor involved is electrostatic interaction between two charges localized on adjacent nitrogen and carbon atom, if no other strong delocalizing group is present.

Ammonium and cycloammonium groups lack stability due to the absence of stabilizing factors. An increase of molecular stability is observed in the cycloimmoniumylides in which the nitrogen atom being involved into N-heteroaromatic ring. The main subject of our studies is the pyridinium, picolinium and benzopyridinium ylides,a class of cycloimmonium ylides in which the cationic part is involved in the heteroaromatic ring.

The stability of pyridinium and benzopyridinium ylides may be attributed to an extensive delocalization of positive charge on the system, as represented by their various contributing structures (13,14) (Scheme IA.3) and to the carbanion participation in the resonance of heteroaromatic ring (14a-c) (Scheme IA.4). The coulombic interactions, which are also responsible for the stability of some ammonium ylides, are less important in case of cycloimmoniumylides so far as the stability is concerened and if it is assumed that there is only an electrostatic interaction between the carbanion and the onium group as represented in the structure (15b), the electron pair of sp^3 hybridized



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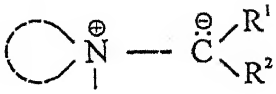

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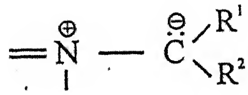

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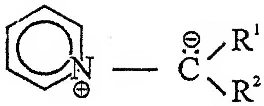

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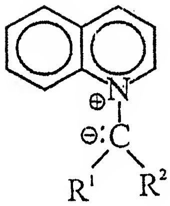
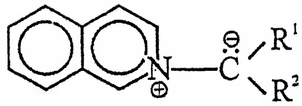


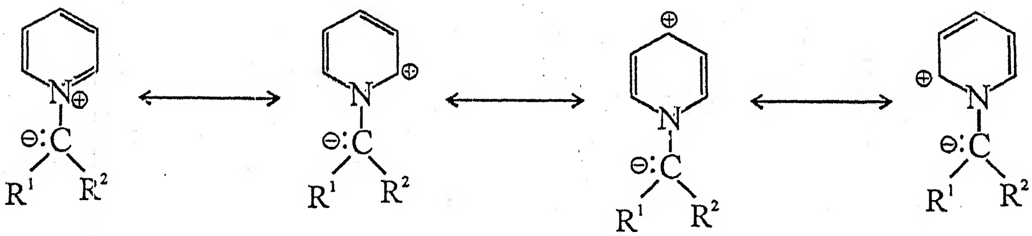
12a



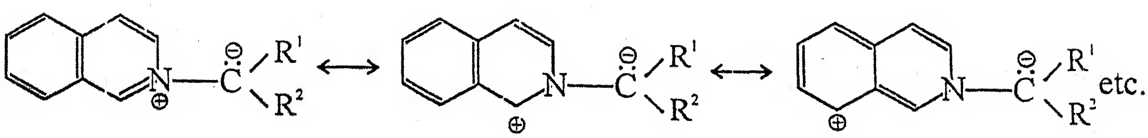
etc.

12b

SCHEME IA.3



13a 13b 13c 13d



14a 14b 14c

ylidic carbanion would be involved in a π–d type of molecular orbital with the sp^2 hybridized nitrogen atom of heteroaromatic ring. However, overlapping is more effective, if we consider the resonating form (15c) in which there is an interaction of the bielectronic p-orbital with the π-electrons of the heteroaromatic ring and therefore, ylides afford stability.[27] The stability has also been found to be influenced by the nature of substituents R^1 and R^2 attached to the ylide carbanion. If these groups are electron withdrawing additional resonance structures occur determining a marked sp^2 hybridization of the ylide carbon through charge delocalization.[27]

The reactivity of cycloimmonium ylides depends on the properties of the carbanion as well as the possible involvement of heteroatom. Usually the alkylidenecycloimmonium ylides of less stability show high reactivity, whereas highly stabilized cycloimmonium ylides show less reactivity. The reactivity of cycloimmonium ylides is influenced by delocalization of positive charge over heteroaromatic ring, coulombic attractive strength between the aromatic positive cyclic nitrogen and the negative carbon and delocalization of charge on the carbon ylide by electron withdrawing groups i.e., R^1 and R^2. Thus, the nucleophilic character of the cycloimmonium ylides decreases while the stability increases if the lone pair of electrons on the α-carbon atom of the form (*14a*) is delocalized. The electron withdrawing substituents R^1 and R^2 tend to stabilize the negative charge and

consequently, reduces the reactivity of the ylide. On the other hand when there is no such interaction, an extremely reactive ylide is formed.

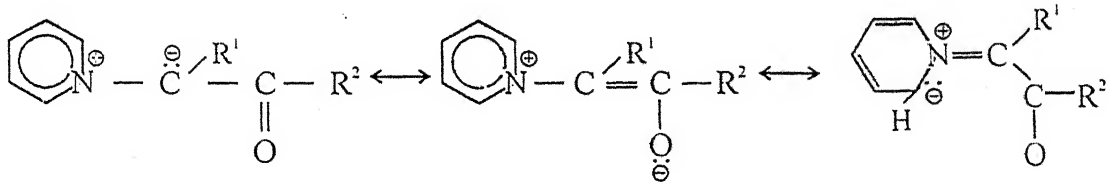
IA.1 Preparation of Cycloimmonium Ylides (Pyridinium ylides)

A.1.1 Ylides from quaternary salt (Salt Method)

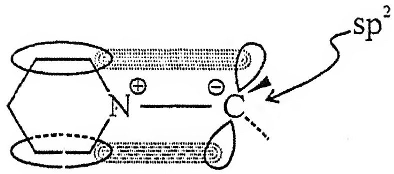
This is the most common method of preparing pyridinium ylides and involves the reaction of quaternary pyridinium salts with a base which is strong enough to abstract a proton from the α-carbon. In principle, any cycloimmonium salt (16) carrying atleast one α-hydrogen is convertable into an ylide (17) (Scheme IA.5).[28,29] Cycloimmonium salts (16) are prepared by the quaternization of substituted alkyl halides with respective tertiary bases viz., pyridine, picoline, quinoline and isoquinoline etc. (Scheme IA.5). Quaternization may also be performed by the treatement of tertiary base with an active methylene derivative and iodine. This method was first reported by Ortoleva[30,31] and widely applied in a large number of cases by King[32-34] and others[35], known as King-Ortoleva method and results in the formation of the quaternary iodide salt of type *(18)* (Scheme IA.6).

The strength of base necessary for the dehydrohalogenation of the corresponding salt depends on the acidity of α-hydrogen atom which, in turn, depends on the nature of substituents present on the α–carbon atom. Most common bases used for the purpose are aqueous

SCHEME IA.4

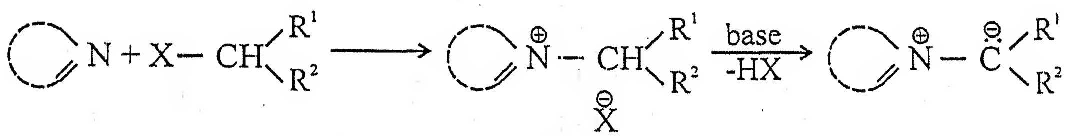


15 a   15 b   15 c



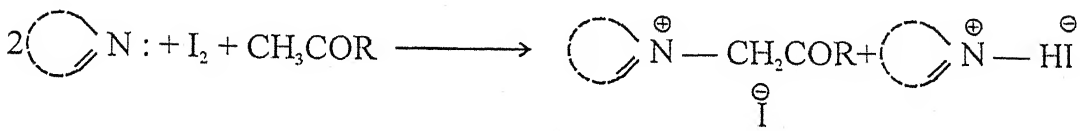
M.O. of 15 c   M.O. of 15 b

SCHEME IA.5



16   17

SCHEME IA.6



18

solution of alkali carbonates[35,35] or amines in anhydrous aprotic solvents.[36-38] Sometime, the use of sodium hydride in dimethylformamide has found to be advantageous, particularly for unisolable ylides which are to be used in subsequent reactions. A wide number of cycloimmonium ylides are incapable of being isolated due to their sensitivity towards atmospheric components and therefore, generated in anhydrous media under inert atomsphere and used as such in subsequent reactions. Such reactions are usually carried out in nonpolar solvents, though some time more polar solvents are advantageous.[39,40]

1.1.2 Ylides from Azaheterocycles and Ethylene Oxide

Linn et al.[41] and others[42] have reported the formation of many dicyanomethyl ylide (21) which are highly stable, by the reaction of tetracyanoethylene oxide (20) with azaheterocycles (19) at 0^0C (Scheme IA.7).

A.1.3 Ylides from Diazo Compounds

Pyridinium ylides (23) have also been prepared by the irradiation of triphenyl or tetraphenyldiazocyclopentadiene (22) in pyridine under nitrogen with a high pressure of mercury lamp through a pyrex filter[43] (Scheme IA.8).

A.1.4 Ylides from *N*-heterocycles and Carbene

Cycloimmonium ylides (25) have also been prepared by the reaction of carbene (24) on azaheterocycles[44] (Scheme IA.9).

A.1.5 Synthesis of Disubstituted Ylides

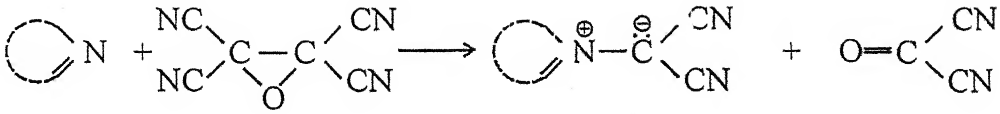
Disubstituted ylides (27,28) have been synthesized from monosubstituted ylide (26) directly by treatment with acylating reagent,[45] isocyanates [46,47] and isothiocyanates[48,49] (Scheme IA.10).

Recently, Leonte and Zugravescu[50] have synthesized dicyanopyridiniummethylide (30) by heating cyanocarbamylpyridinium-methylide (29) with $POCl_3$ in the presence of sodium pyrosulfide. But when acetic anhydride was used as dehydrating agent instead of $POCl_3$, cyanoacetylpyridinium-methylide (31) was formed. The ylide (31) was also prepared by acetylation of ylide (32). Alternatively, ylide (30) could be synthesized by the reaction of bromocyano-acetic ester (33) with carbalkoxypyridinium-ylide (34) (Scheme IA.11).

A.1.6 Synthesis of Polyylides

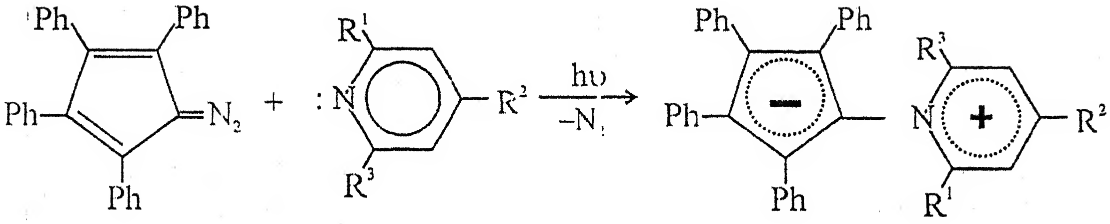
Although numerous methods have been devised from time to time to enable the synthesis of mono and disubstituted ylides [45-50] as described in the previous section, yet no attention has been paid towards synthesizing poly-ylides for nearly two and a half decade since the inception of pyridinium ylides. It was during early seventies that Berlin et. al. [51,52] and others[53] shared the credit for synthesizing poly ylides by dehydrohalogenation of poly (4-methylpyridinium chloride) (35) in the presence of aqueous ammonia and demonstrated the formation of polyylide (36) by appearance of a dark coloured water insoluble polymeric product (Scheme IA.12).

SCHEME IA.7



19 20 21

SCHEME IA.8



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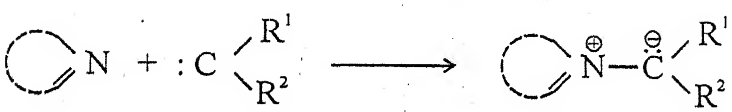
SCHEME IA.9



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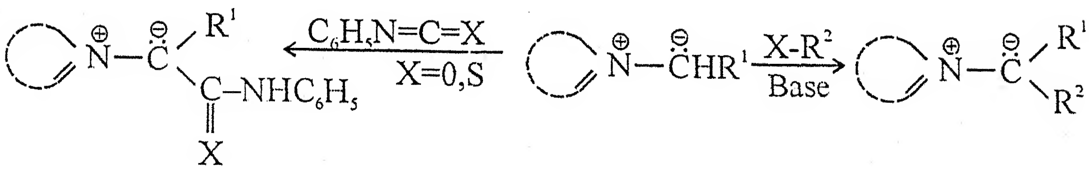
SCHEME IA.10



28 26 27

IA.2 Reactions of Cycloimmonium Ylides (Pyridinium ylides)

A.2.1 Thermolysis

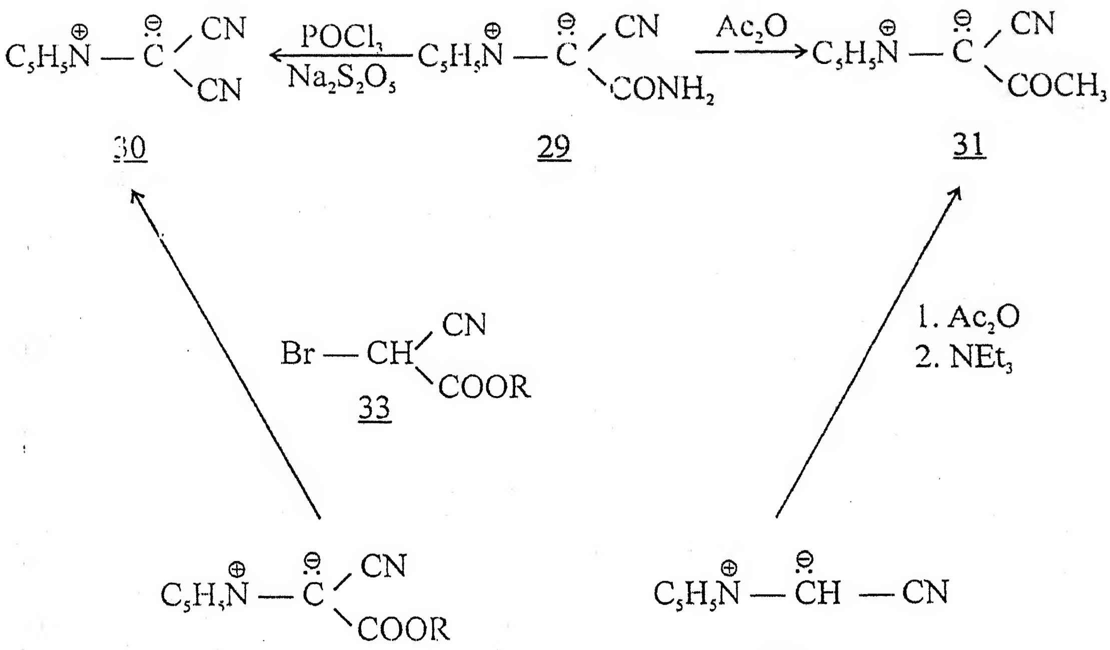
The thermal stability of cyclommonium ylides considered as a criterion of molecular stability was not studied in adequate experimental conditions. Cook et al.[54] isolated dibenzoylethylene (37) by sublimation of pyridinium ylide (12) at 150°C in high vacuo conditon. The former product (37) seemed to have been resulted from dimerization of carbene intermediate formed by the heterolytic cleavage of ylide bond, however, the reaction took another course when the same ylide (12) was heated in benzene in presence of copper or copper oxide to afford 1,3-dibenzoylindolizine[55] (38) unexpectedly. The mechanism of the reaction is still obscure (Scheme IA.13).

Zugravescu et al.[56] have studied the thermal decomposition of mono and disubstituted isoquinolinium ylides (39) and reported the formation of isoquinoline and cyclopropane derivatives (41), formed by trimerization of carbene intermediate (40) (Scheme IA.14).

A.2.2 Photochemistry

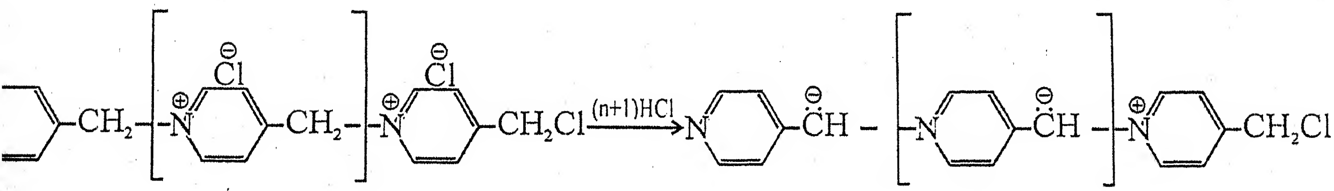
The existing literature reveals that no considerable amount of work has been done on the photolytic conversions of pyridinium ylides.[57,58] However, these ylides (42) in the presence of ultraviolet radiations usually follow two different courses: (i) the cleavage of $>\overset{\ominus}{C}-\overset{\oplus}{N}$ bond with the formation of the heterocycles and disubstituted

SCHEME IA.11



30 29 31 33 34 32

SCHEME IA.12



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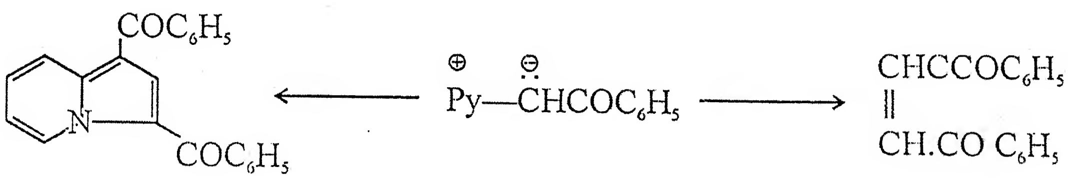
SCHEME IA.13



38 37

carbene which in turn, add on benzene to give benzene- norcaradiene (44). This is usually the main reaction and (ii) the photochemical isomerisation of the ylide, involving either contraction or expansion of heteroaromatic ring (43) (Scheme IA.15).

A.2.3 Alkylation

Cyclcimmonium ylides having active methylene group are capable of undergoing substitution reaction with alkyl halides to afford carbanion disubstituted ylides (46), presumably via intermediacy of salt (45) which in the presence of base looses hydracid molecule and converted into the ylide[59] (46) (Scheme IA.16). However, the method was found to be of little worth in the syntheses of disubstituted ylides owing to the fact that they undergo decomposition.

If alkylation is carried out without using dehydrohalogenating reagent, the overall process is rather complex. Thus, by treating pyridiniumbenzoyl methylide (12) with phenacyl bromide, owing to the possible interaction between the intermdiates and the initial ylide (12), and to the transylidation reaction and bond cleavage, gave several products[60] (47-51) (Scheme IA.17).

Henerick et. al.[61] reported the preparation of a wide range of ketones (54) by the reduction of salt (53) with zinc and acetic acid, formed by the alkylation of ylide (52) (Scheme IA.18).

A.2.4. Acylation

Cycloimmonium ylides (55), due to strong nucleophilicity of the ylide carbanion, can be easily acylated by a suitable acylating agent (Scheme I.A.19). However, the course of the reaction varies with the nature of acylating agent used. Thus, pyridinium ylide (56) with benzoyl chloride led to the O-acylated (57) and S-acylated products[62] (58), whereas with benzoic anhydride only C-acylated products (59) are obtained [60,38] (Scheme IA.20).

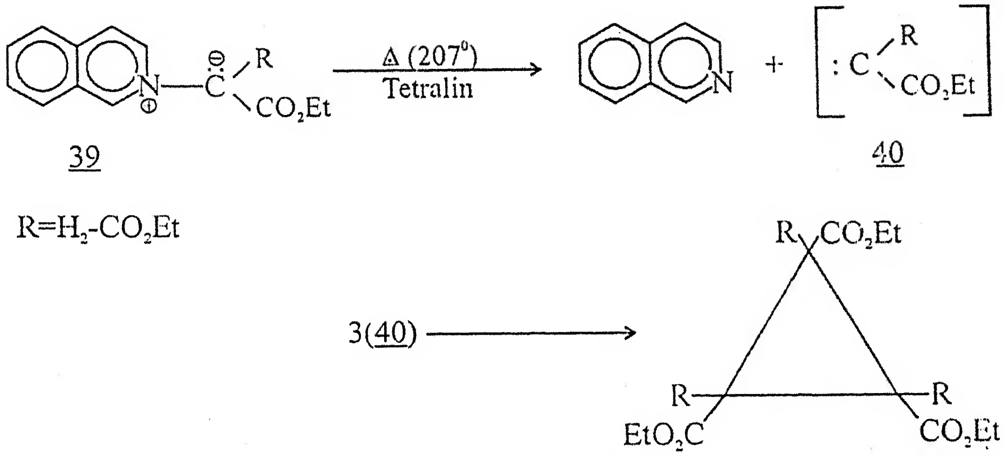
Similarly, the interacation of the isoquinolinium ylides (60) with benzoic anhydride led to the formation of C-acylated products[63,64] (61) only (Scheme IA.21).

A.2.5 Arylation

Unlike alkylation reactions, the arylation of cycloimmonium ylides is comparatively difficult due to diminished reactivity of aryl halides. However, Reusching and Krohnke[65] reported that quinolinium-ylides (62) when subjected to arylation by picryl chloride (63) forms through an intermediate (64) a red coloured product to which structure (*65*) is assigned. The same on treatment with concentrated sulphuric acid undergoes debenzoylation resulting in the formation of 8,10-dinitrosoindole (2,1-a) quinoline (66) (Scheme IA.22).

Similarly, pyridinium and isoquinolinium ylides (67a,b) also react 'in situ' with picryl chloride (63) in alkaline media to afford deep coloured products to which structures (68a,b) were assigned. Furthermore, it was observe that the products (68a, b) on their treatment with piperidine lose a

SCHEME IA.14

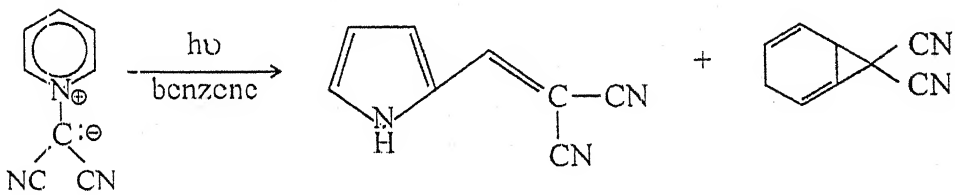


39 40

R=H$_2$-CO$_2$Et

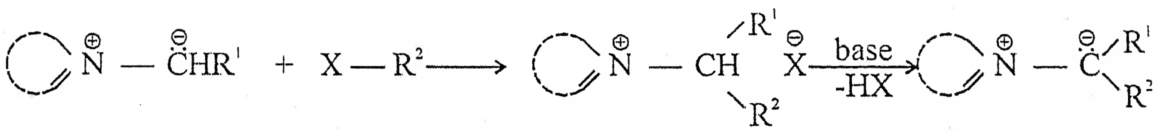
41
R=H$_2$-CO$_2$Et

SCHEME IA.15



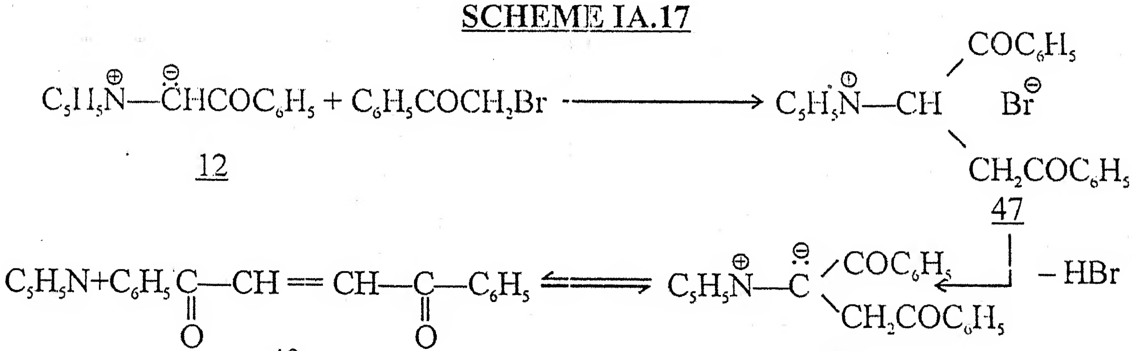
42 43 44

SCHEME IA.16



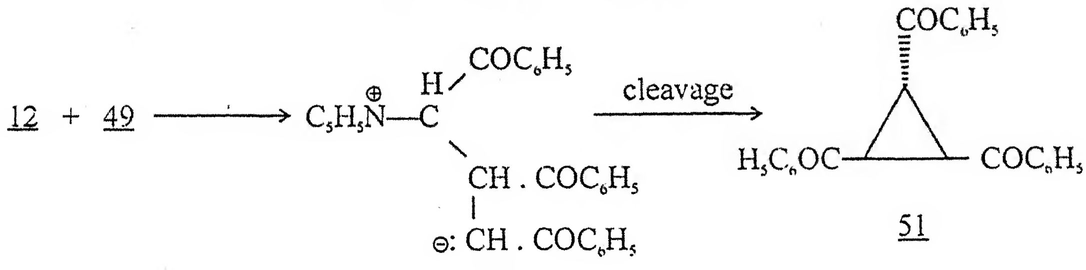
45 46

SCHEME IA.17



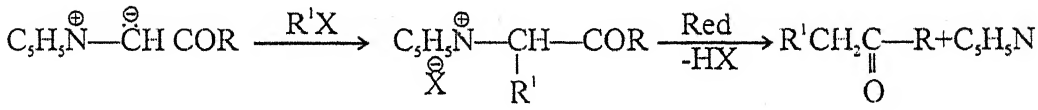
12 47 48 49

Conti.. SCHEME IA.17



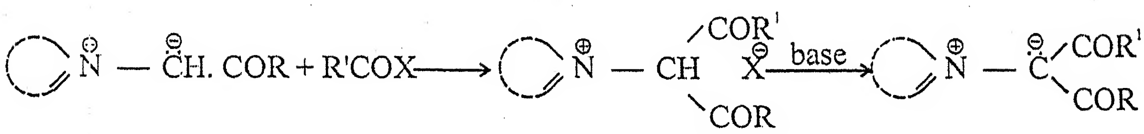
50 51

SCHEME IA.18



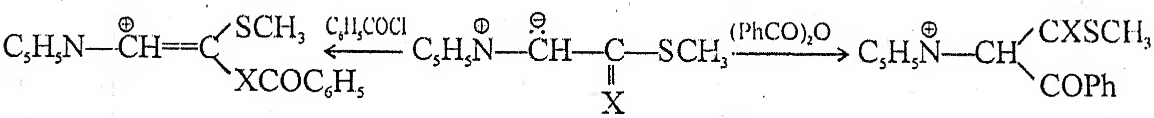
52 53 54

SCHEME IA.19



55

SCHEME IA.20

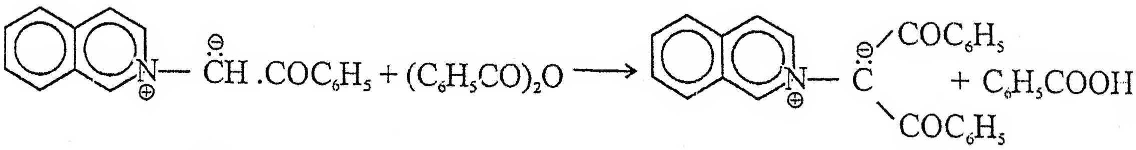


57 – 58 56 59

57 ; X = O

58 ; X = S

SCHEME IA.21



60 61

molecule of nitrous acid, thus leading to the formation of indolizines (*69a,b*) (Scheme IA.23).

A.2.6 Reaction with Aldehydes

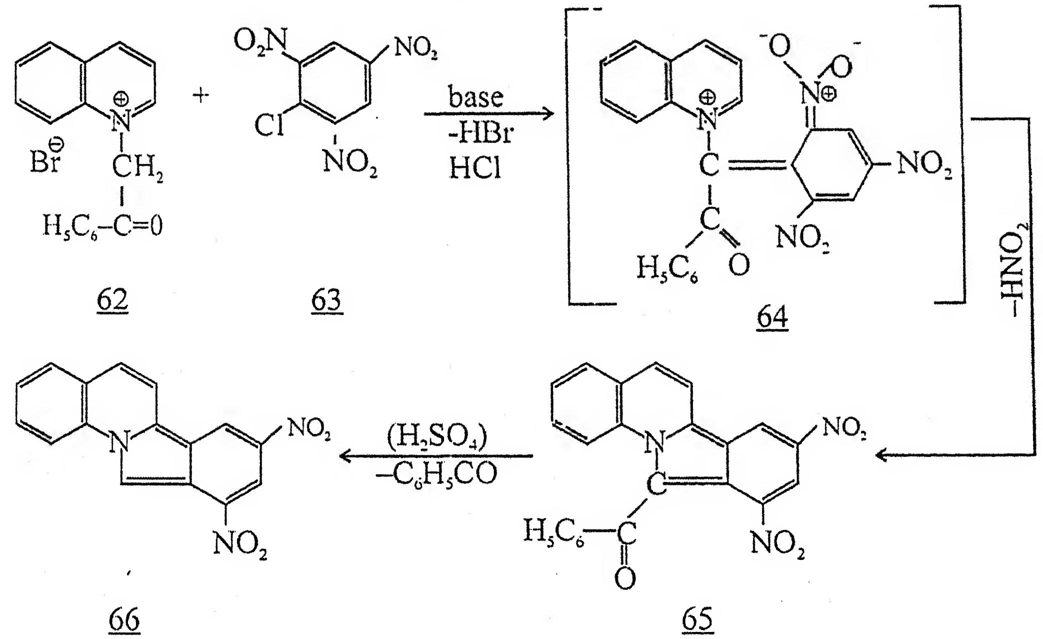
Pyridinium-ylides react with aldehydes to afford aldol type products as a pyridinium ethanolic salt (70)[66,67] (Scheme IA.24). Howe and Ratts[68] reported the deuterium exchange studies in the piperidine catalyzed condensation of *N*-methylpyridinium iodide (71) with aromatic aldehydes and observed that N-(2-hydroxy-2-phenylethyl) pyridinium iodide (73) is formed along with 2- (α-hydroxybenzyl)- 1-methylpyridinium iodide (72) (Scheme IA.25).

Pyridinium-ylides, generated from pyridinium salt (74) having strong electron withdrawing groups readily react with aromatic aldehyde in the presence of pyridine to afford vinylpyridinium salts[69] (75) (Scheme IA.26).

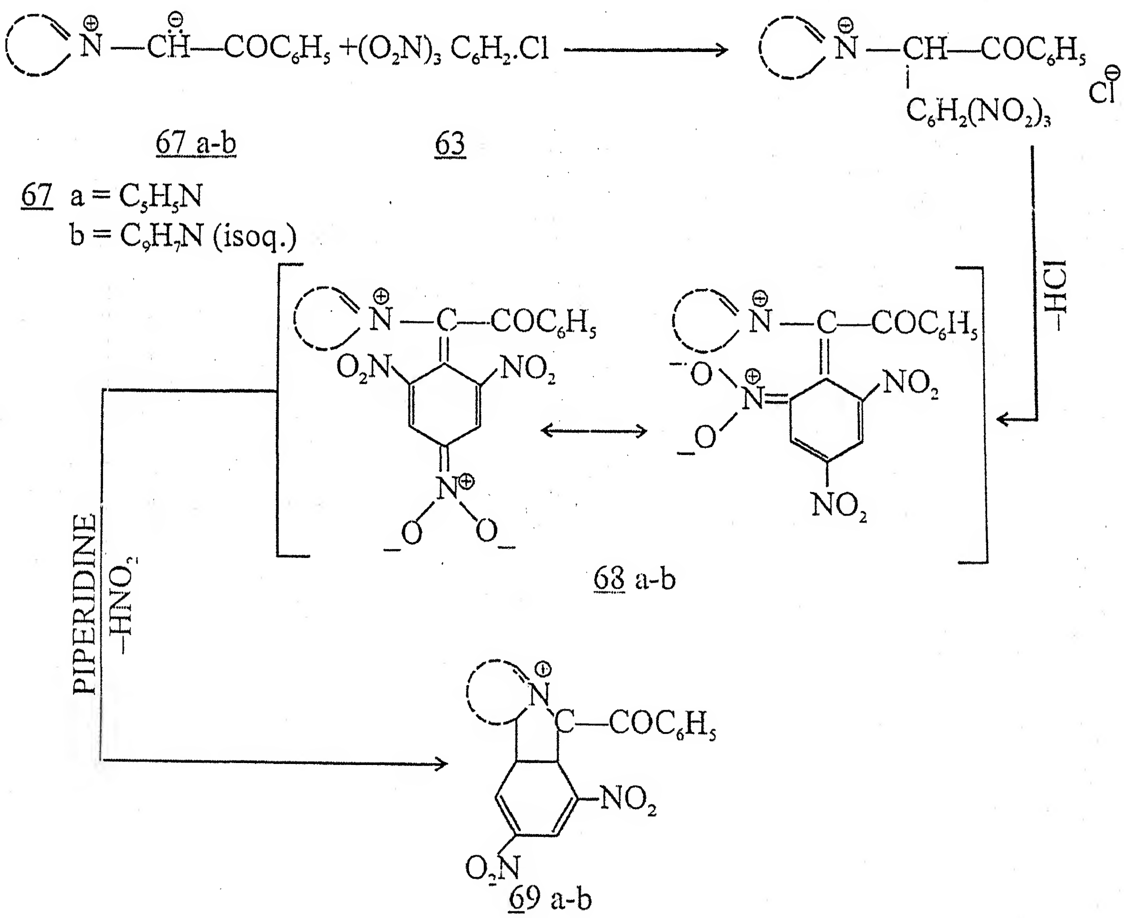
Pyridinium-ylides, when treated with aromatic aldehydes in the presence of ammonia, undergo Mannich type of condensation to afford pyrimidines. Thus, phenacylidene pyridinium-ylide (76) reacts with aromatic aldehydes in the presence of glacial acetic acid and ammonia to afford triarylpyrimidines[69] (77) (Scheme IA.27).

Unlike pyridinium ylide, there are very few reports concerning the reaction of aromatic aldehydes with isoquinolinium ylides. However, Ahlbrecht et al.[67] were first to report the reaction of semistabilized isoquinolinium ylide (78) with aromatic aldehydes to afford corresponding isoquinolinium ethanols (80) via intermediacy of compound (79) (Scheme IA.28).

SCHEME IA.22



SCHEME IA.23

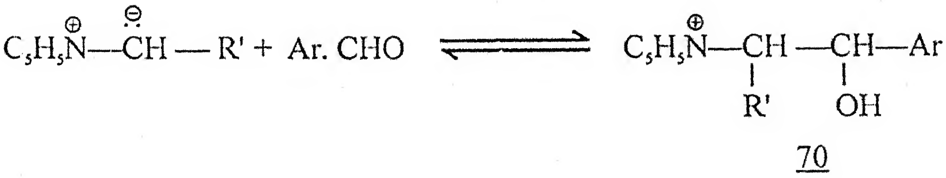


A.2.7 Reaction with Ketones

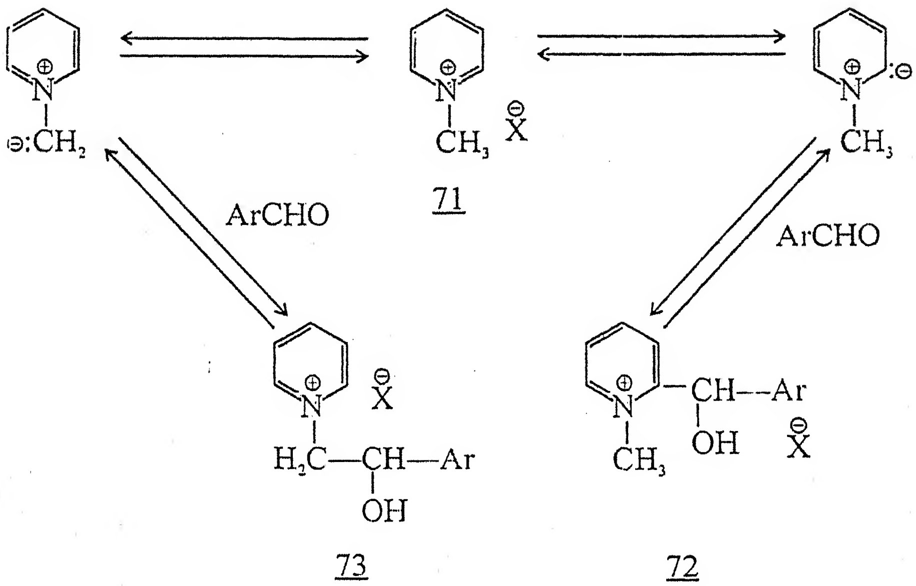
The reactions of cycloimmonium ylides with carbonyl functions are not only restricted to the aldehydes but the same are also found to be quite reactive towards ketones as evidenced by their reactions with tropone, 1,2-diketone and quinone etc. However, the mode of reaction depends upon the nature of the ylide as well as on the ketone employed for the purpose. Thus, phenacylidenepyridinium ylide (81) reacts with tropone to afford 2-hydroxy-2-pheynyl-3-phenacyl-2H-cyclohepta (b) furan[70] (82) (Scheme IA.29).

Contrary to this, pyridinium ylides may take a different course when they are made to react with 1,2-diketone. This approach was proved to be highly indispensable in the syntheses of heterocycles. Noteworthy in this respect, is the synthesis of 2,3-disubstituted dehydroquinolinium salt (84) through the condensation of 2-picolinium salt (83), carrying an activated N-pyridinoylmethyl group, with 1,2-diketone in the presence of weak base[71] (Scheme IA.30). This reaction in the later stage proved to be highly useful for the comprehensive synthesis of quinoline ring[72] particularly useful in building up of alkaloid nucleus. Pyridinium ylides were also found to undergo reaction with quinone resulting in the formation of heterocycles, which, in turn, depends upon the cyclization agent. Thus, pyridinium ylide reacts '*in situ*' with 2-chloro-1, 4-naphthaquinone following Michael type of addition to afford an intermediate (85) which on cyclization in the presence of zinc and acetic acid gives benzocoumarine (86). However, benzocinnoline (87) is the exclusive

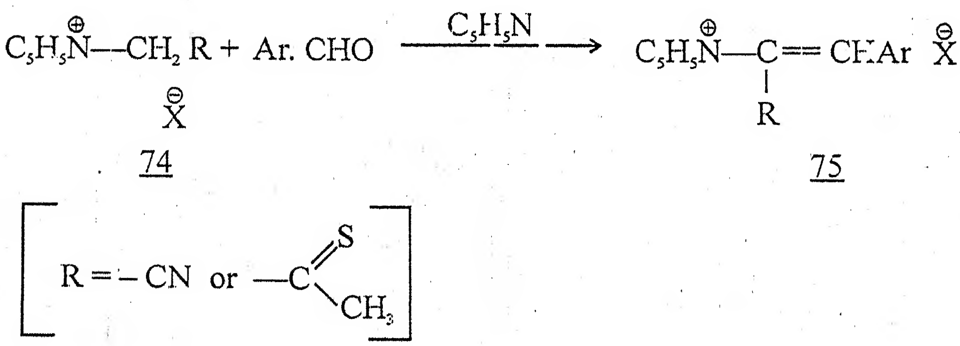
SCHEME IA.24



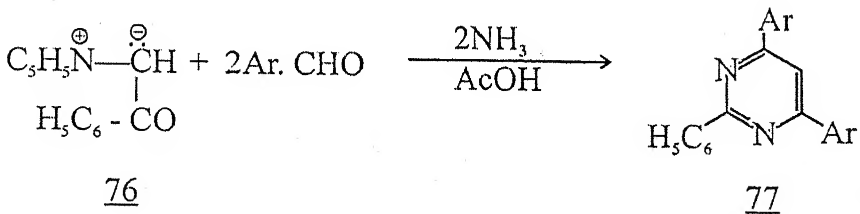
SCHEME IA.25



SCHEME IA.26



SCHEME IA.27



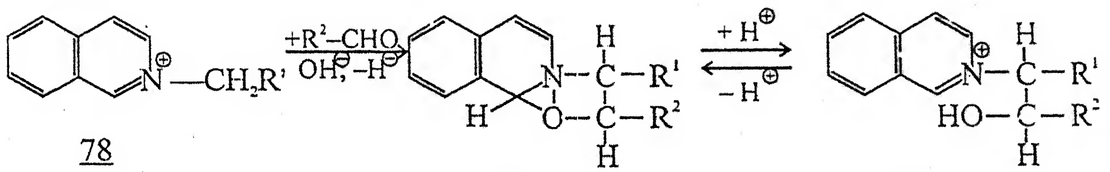
product of the reaction when hydrazine hydrate is employed for bringing about aza ring closure of the intermediate product (85)[73,74] (Scheme IA.31).

A.2.8 Reaction with α,β-Unsaturated Ketones

A variety of *N*-heterocycles as well as aromatic hydrocarbons may be synthesized by the reaction of cycloimmonium ylides with α,β-unsaturated ketones owing the different course of the reaction, which, in turn, depends both upon the experimental conditions as well as on the nature of ylide employed for the purpose. Thus phenacylidenepyridinium ylide and their isoquinolinium counterparts (88a,b), generated **'in situ'** from thei· respective precursors, readily add on α,β-unsaturated ketones to afford pentane&1,5-dionylpyridinium and isoquinolinium derivatives (89a-b) which on treatment with a mixture of glacial acetic acid and ammonium acetate undergo aza ring closure to afford 2,4,6-trisubstituted pyridines[71,75,76] (90) (Scheme IA.32) whereas α-pyridones[77] were the exclusive products of Michael addition followed by cyclization of *N*-(aminoformylmethylene)pyridinium ylide (91) on α,β-unsaturated ketones (Scheme IA.33). Krohnke et al.[75] have applied this method in the syntheses of a variety of useful pyridines and pyridones.

Pyridinium salts (93) with active methylene group, when treated with substituted benzalacetophenone (94) in the presence of anhydrous zinc chloride, afforded polycyclic aromatic hydrocarbons[74,78] (95) (Scheme I.34).

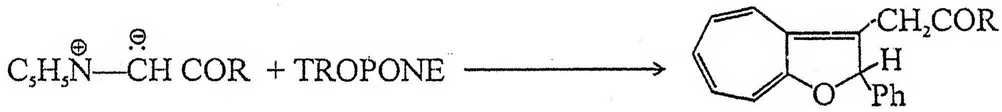
SCHEME IA.28



78 79 80

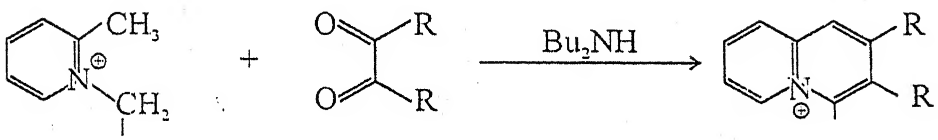
$R^1 = -C_6H_5$
$= 4-NO_2C_6H_4$.

SCHEME IA.29



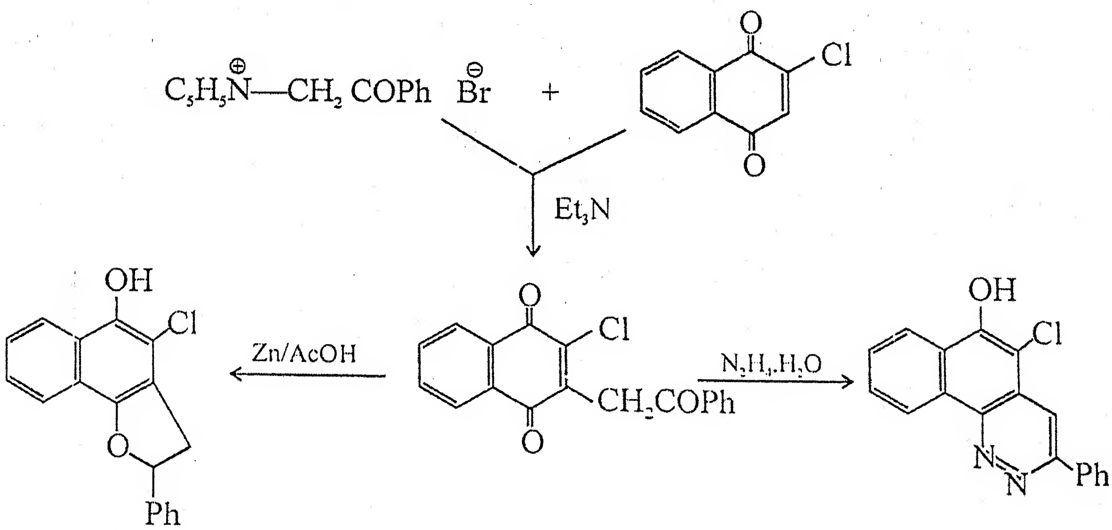
81 82

SCHEME IA.30



83 84

SCHEME IA.31



86 85 87

A.2.9 Reaction with Nitroso Compounds

Krohnke et al.[79-80] were first to report that the cycloimmonium ylides are capable of undergoing reaction with nitroso compounds to afford nitrone derivatives. Thus, the pyridiniumphenacylides and their isoquinolinium counterparts (96a,b) generated from their precursors, on reaction with nitroso benzene afforded similar product, α-benzoyl-N-phenyl-nitorne (97) inspite of different onium centre (Scheme IA.35).

The reaction of 4-bromophenacyl idenepyridinium ylide (98) with α-nitroso-β-naphthol and α-nitroso-β-naphthylamine was found to afford naphthoxazole derivative (99) and benzoquinoxaline-N-oxide derivative (100) respectively[81] (Scheme IA.36).

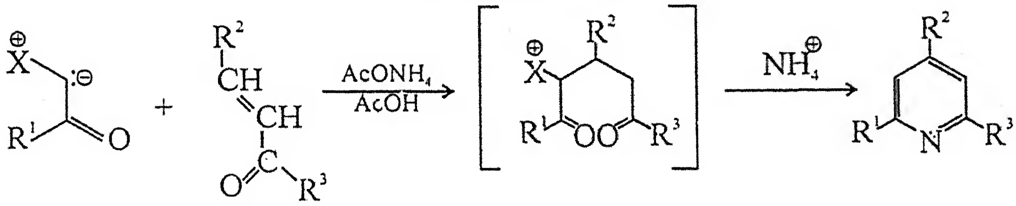
A.2.10 Reaction with Carbon-Sulfur Bond

Phenacylidenepyridinium ylide (101) reacts with carbon disulfide to afford S-betaine (102) which on treatment with methyl iodide gives s-alkylated product (103)[82,83] (Scheme IA.37). On the other hand, phenacylideneiso-quinolinium-ylide (104) reacts with carabon disulfide in alkaline medium to afford 2-mercapto-3-benzoylthiazole [2,3-a] isoquinolinium ring system (105) proving stronger positivation of list position in comparison to the above mentioned pyridinium ylide[84] (Scheme IA.38).

A.2.11 Reaction with Nitrile-Imine

It has been observed that reaction of cycloimmonium ylides with dipolar species takes an interesting course mainly due to the fact that they are polarisable molecules and their reactions are markedly influenced by the nature

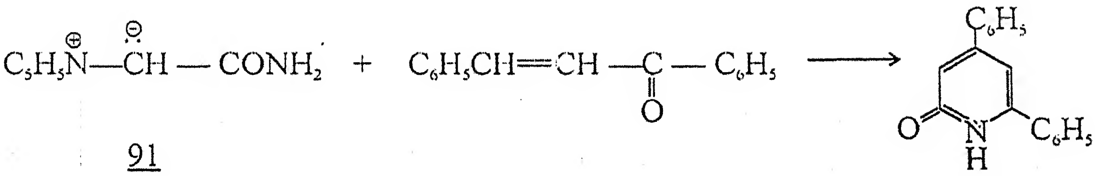
SCHEME IA.32



88 a-b   89 a-b   90

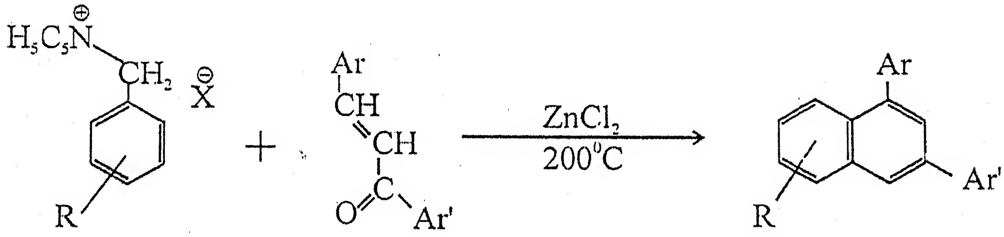
a X= C_5H_5N
b X=C_9H_7N

SCHEME IA.33



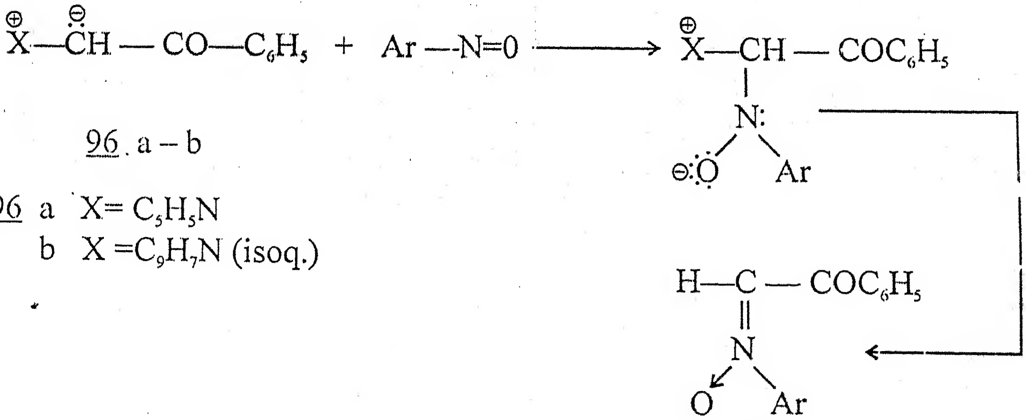
91   92

SCHEME IA.34



93   94   95

SCHEME IA.35



96 . a – b

97

96 a X= C_5H_5N
b X =C_9H_7N (isoq.)

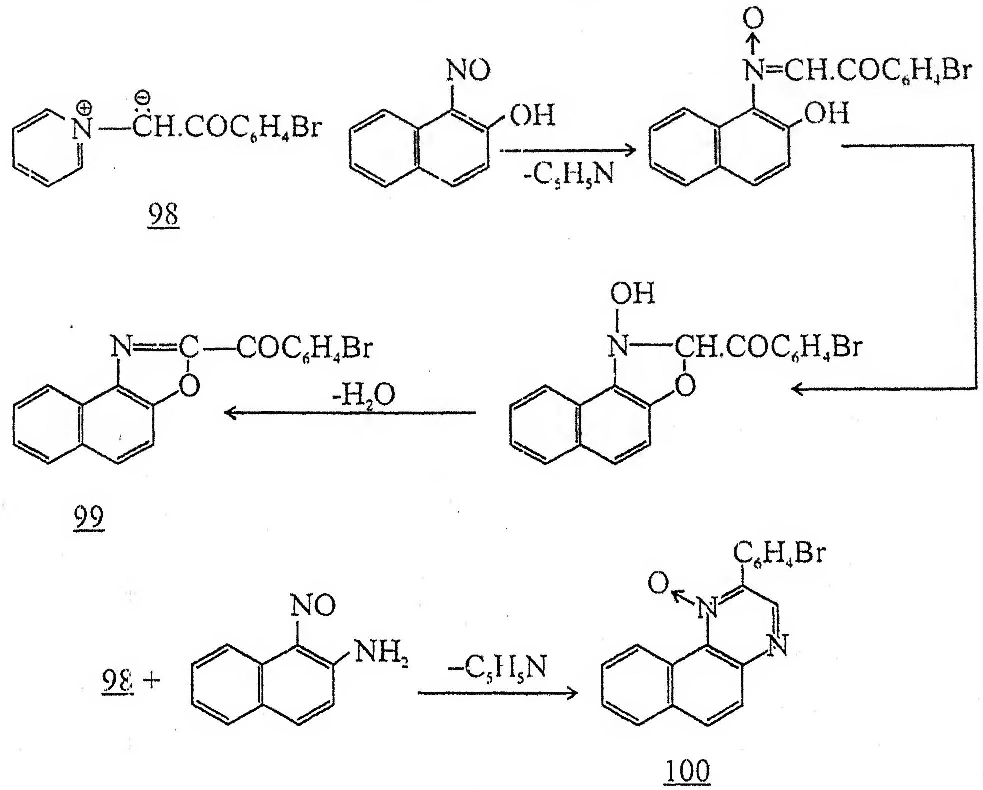
of solvent and base employed for their generation. Thus, pyridinium phenacylide, when generated 'in situ' from sodium methoxide in dioxane-methanol medium, reacts with nitrile imine to afford the adduct (106). On the other hand, reaction follows an entirely different course when triethylamine in chloroform is used as base and gives a mixture of products (107) and (108) (Scheme IA.39).

1.2.12 Reaction with Nitromethane

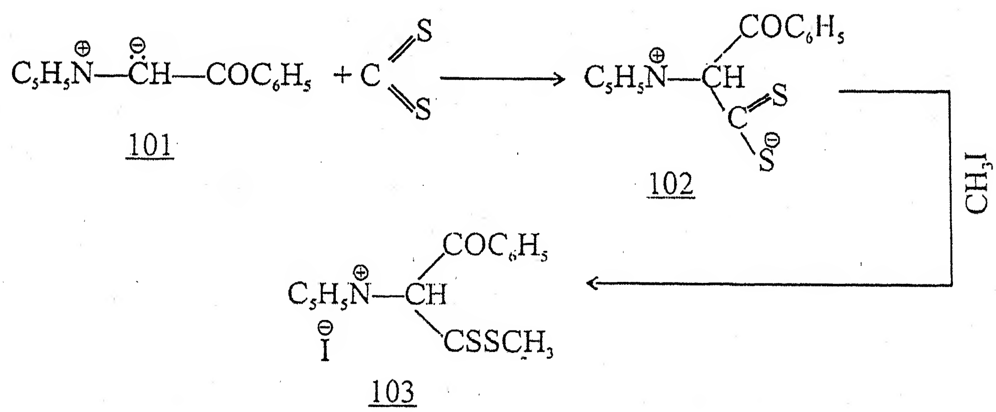
Keil and Krohnke[86] studied the cyclization reaction of isoquinolinium-ylides (109a) generated 'in situ' from the respective precursors by using sodium carbonate as dehydrohalogenating agent and reported the formation of two products (113a) and (114) via intermediacy of (112), formed by dehydration of another intermediate (111), formed by the internal aldolization of primary reactions products (110). However, the compound (113b) was the exclusive product of the reaction of nitromethane and isoquinolinium ylide when triethlamine was used as dehydrohalogenating agent instead of sodium carbonate (Scheme IA.40).

It is interesting to note that neither N-acetonyl nor N-phenacylidenepyridinium ylides, themselves, are capable of undergoing similar cyclization reactions with nitromethane as isoquinolinium ylides, but the substitution of cyano group at position 3 in the pyridiniums ring makes the pyridinium ylide as reactive as isoquinolinium ylide. Thus pyridinium ylide (115) reacted with nitromethane resulting in the formation of indolizine derivative[87] (166) following the same reaction sequence (Scheme IA.41).

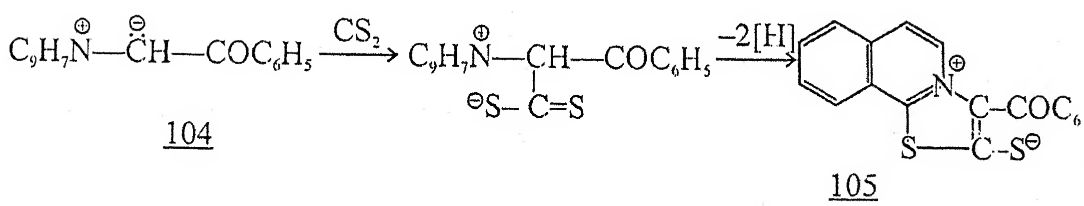
SCHEME IA.36



SCHEME IA.37



SCHEME IA.38



A.2.13 Reaction with Diazonium Salts

Substituted aroylmethylene pyridinium ylides (101) are capable of undergoing reaction 'in situ' with diazonium salts, obtained from aromatic acids to afford 1,4-dihydro-1,2,4,5-tetra-zines (117)[88] in the presence of sodium acetate (Scheme IA.42).

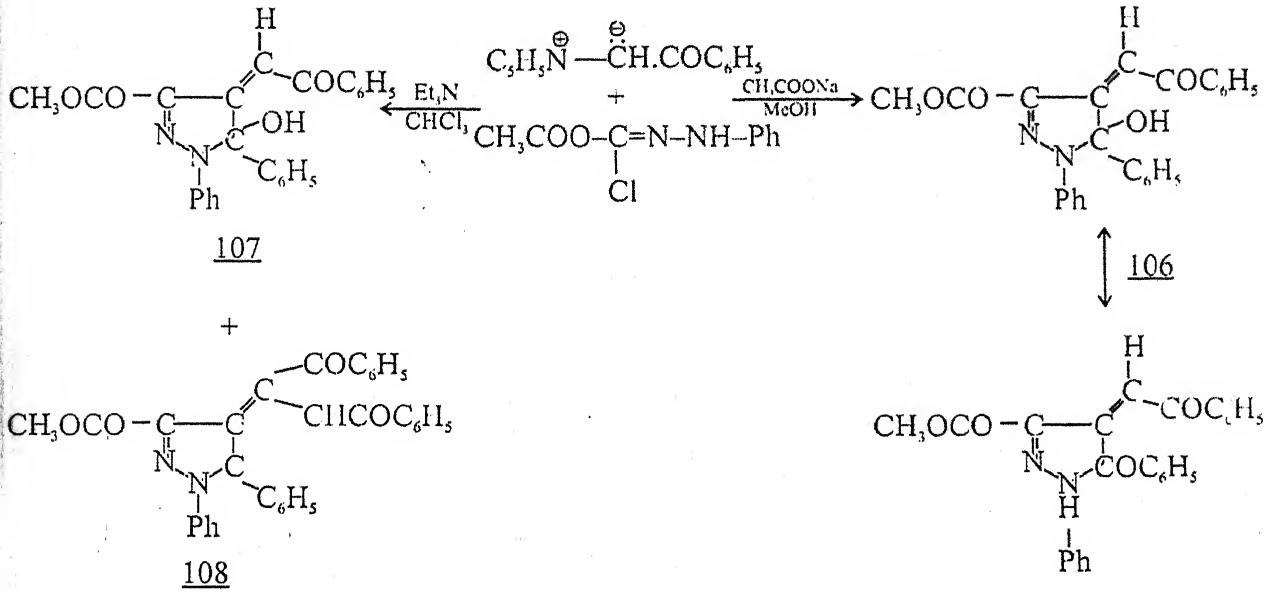
A.2.14 Reaction with Amino Compounds

Cycloimmonium ylides are capable of undergoing reaction with amino-compounds in a variety of ways depending on the chemical nature of amino-compounds and ylide employed for the purpose. Thus, pyridinium ylide (118a) with aliphatic amines[89] forms respective imidopyridinium salt (119). On the other had, 3-cyanosubstituted pyridinium ylide (118b) due to strong positive charge at α-position, undergoes cyclization reactions with hydrazine hydrate to afford cyclopyridinotriamine[90] (120) (Scheme A.43).

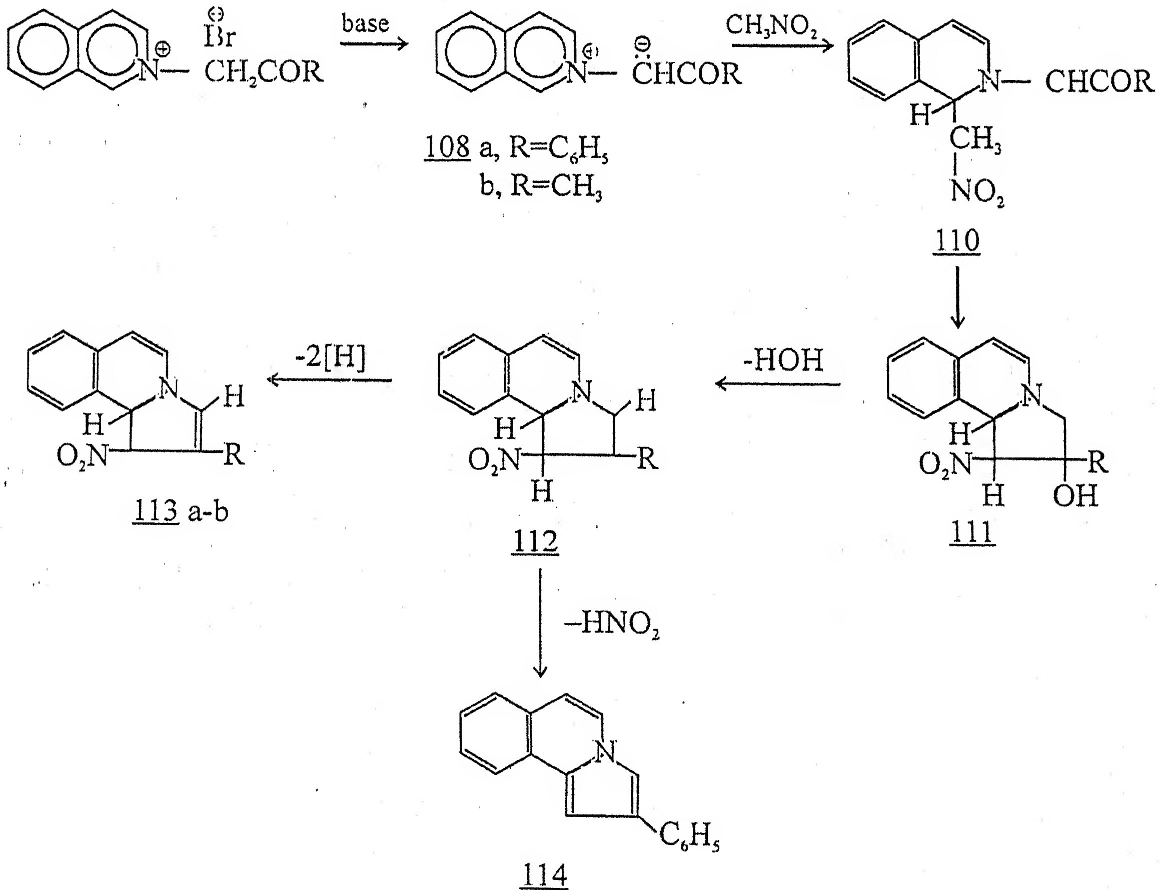
Aroylmethylenepyridinium ylides and their isoquinolinium counterparts (96a-b) react '***in situ***' with aromatic amines[91,92] to afford indole derivatives (121) in the presence of *N, N*-dimethylaniline under reflux temperature. However, ylides when treated with o-phenylenediamine[93] in boiling acetic acid affords 2-phenylbenzimidazole derivatives (122) (Scheme IA.44).

On the other hand, phenacylidenequinolinium ylides (123) on their reaction with aromatic amines and o-phenylenediamine follow a different course of reaction due to the presence of strong positive charge at α-position and thus give rise to the formation of dihydroimidazol [1,2,a] quinolinium system[94] (124a,b) (Scheme IA.45). However, isoquinolinium ylides (125) reacts '*in*

SCHEME IA.39



SCHEME IA.40



situ' with hydrazine hydrate to afford triazinophenanthridine derivatives[95] (126) (Scheme IA.46).

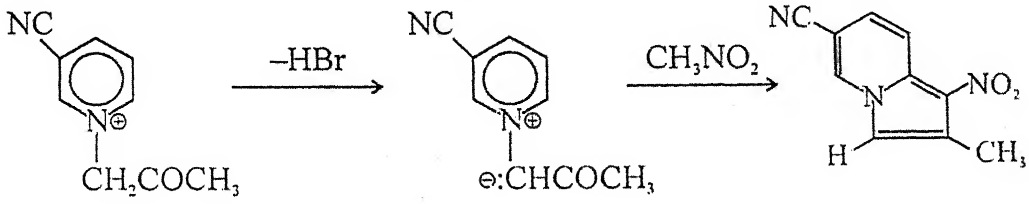
Phenacylideneisoquinolinium ylides (127) and their quinolinium counterparts (128) are capable of undergoing cyclization reactions with ammonia or ammonium acetate[94] in glacial acetic acid to afford 2-phenyl-2, 3-dihydroimidazoisoquinoline (129) and 2-phenyl-1, 2-dihydroimidazo [1,2,a] quinoline (130) showing stronger positivation of onium groups in comparison to that of pyridinium ylides (Scheme IA.47).

1.2.15 Reaction with Isocyanates and Isothiocyanates

Aroylmethylenepyridinium, quinolinium and isquinolinium ylides, due to strong nucleophilic character of the ylide carbanion afforded respective carbanion disubstituted ylide (133) on reaction with phenylisocyanate and isothiocynate (131a,b) via intermediacy of betain derivative[55,96] (132) (Scheme IA.48).

Later on, Soto and Ohta[96] reported that toluene solution of betaine derivative (134a,b) formed by the reaction of phenacylideneisoquinolinium ylide with phenylisocyanate and phenylisothiocyanate (131a,b), when heated under reflux for a longer time in the presence of air gave the mesoionic adducts (135a,b) via a dehydrogenating cyclization. The compounds (135a,b) could easily be methylated with methyl iodide to afford respective methyl derivatives (136a,b) (Scheme IA.49).

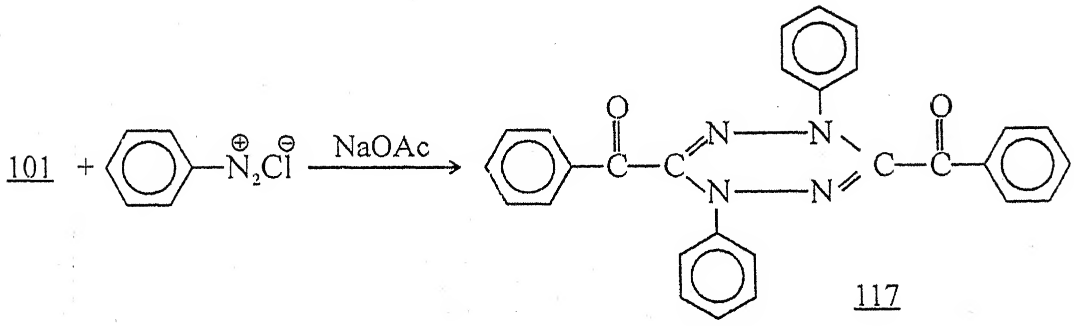
SCHEME IA.41



115

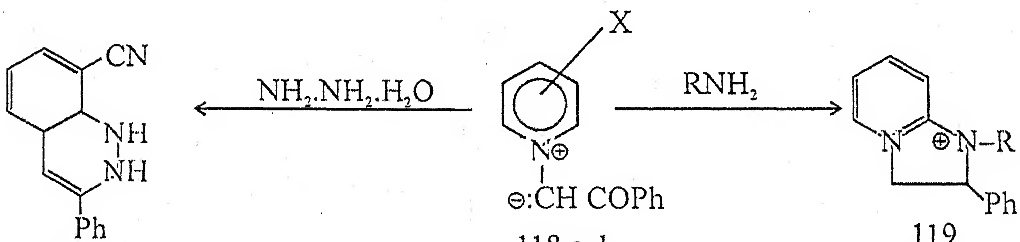
116

SCHEME IA.42



117

SCHEME IA.43



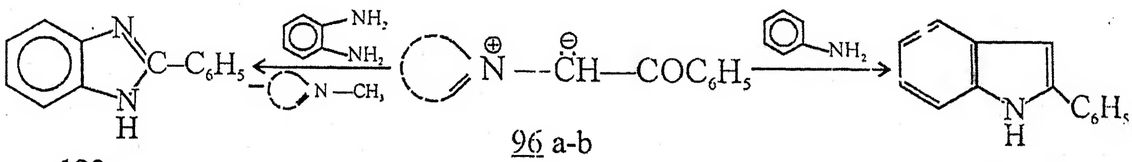
120

118 a–b

119

118 a, X =2–Br
b, X=3--CN

SCHEME IA.44

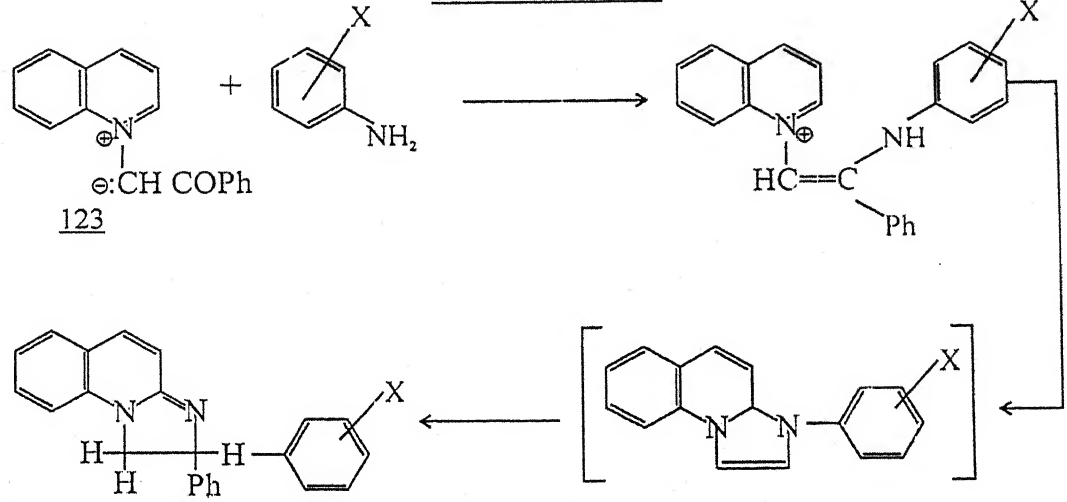


122

96 a-b

121

SCHEME IA.45

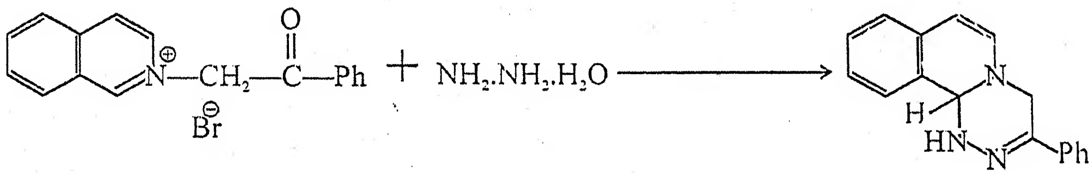


123

123 a–b

124 a, X= H
b, X=2–NH₂

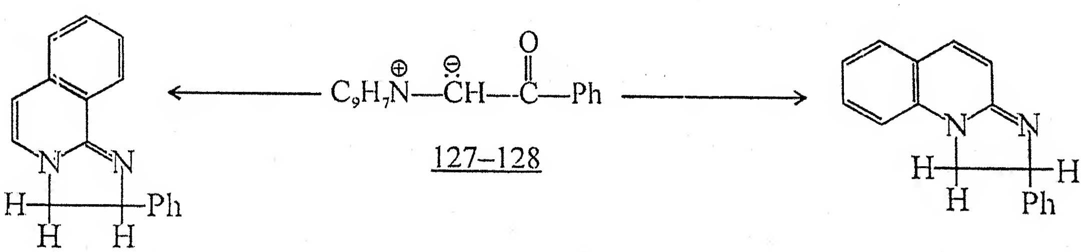
SCHEME IA.46



125

126

SCHEME IA.47



127–128

129

130

A.2.16 Cycloaddition Reactions of Cycloimmonium Ylides

Pyridinium, quinolinium and isoquinolinium ylides undergo various types of cycloaddition reactions to afford heterocyclic compounds which are difficult to prepare via other synthetic routes[99-114].

(i) Dimerization reaction

Isoquinolinium salts (137) in basic tetrahydrofuran or chloroform are converted into dimers (139). The formation of these dimers are attributed into a (3+3) cycloaddition of intermediate ylide[97-98] (138) showing 1,3-dipolar nature (Scheme IA.50).

(ii)(3+2) Dipolar cycloaddition reactions

(a) Reactions of monosubstituted ylides with acetylenic derivatives-

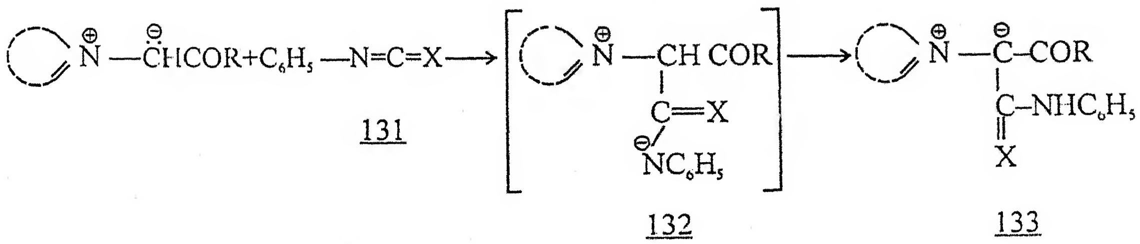
Monosubstituted pyridinium ylides (140) undergo cycloaddition reactions with acetylenic dipolarophiles (141) giving indolizines (143). The primary addition product (142) easily aromatise either by hydrogen transfer to the dipolarophile[99-101] or by dismutation[102] (Scheme IA.51).

The isoquinoliniummethylides (144) react almost in a similar manner with acetylenic dipolarophiles and gives benzoindolizines (147) formed by the aromatization of the intermediates dihydroindolizines (145,146) (Scheme IA.52). The mono-substituted quinoliniumylides behave in exactly similar manner to that of pyridiniumylides.

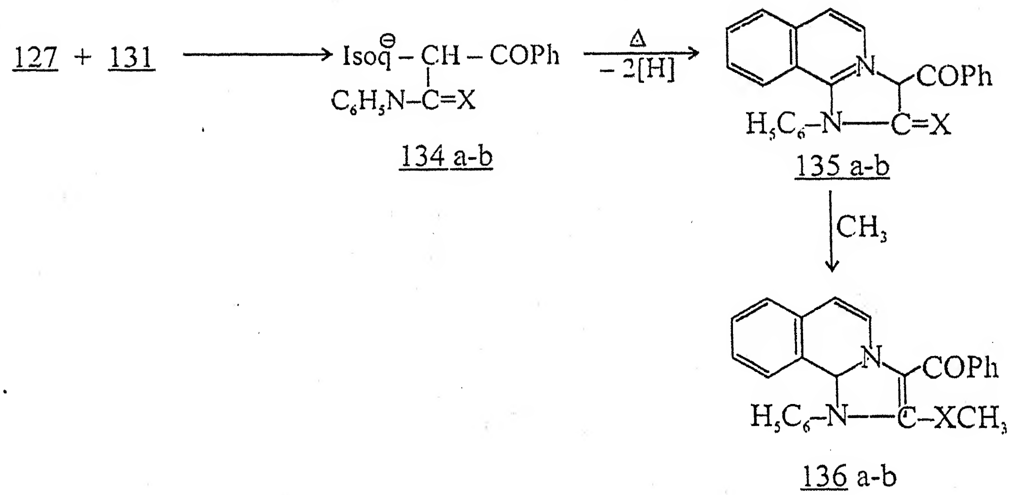
b) Reaction of disubstituted ylides with acetylenic dipolarophiles-

The disubstituted ylides give (3+2) type of cycloaddition reactions

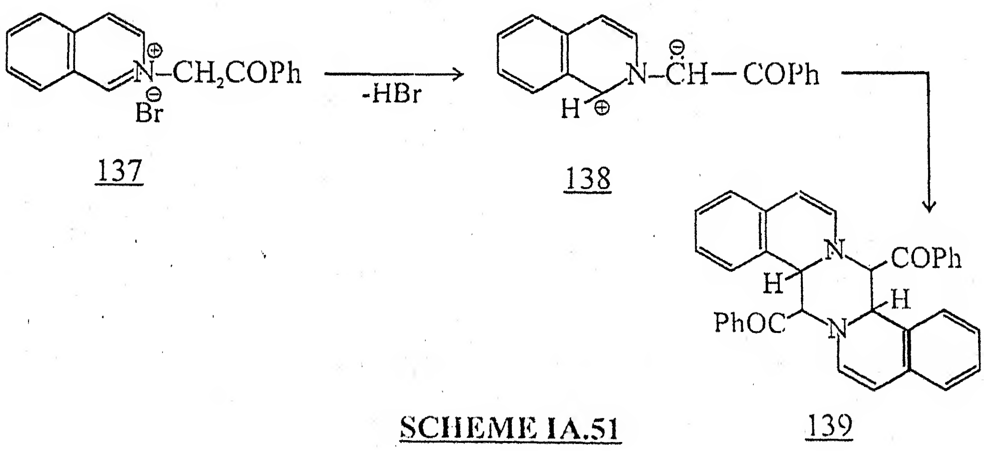
SCHEME IA.48



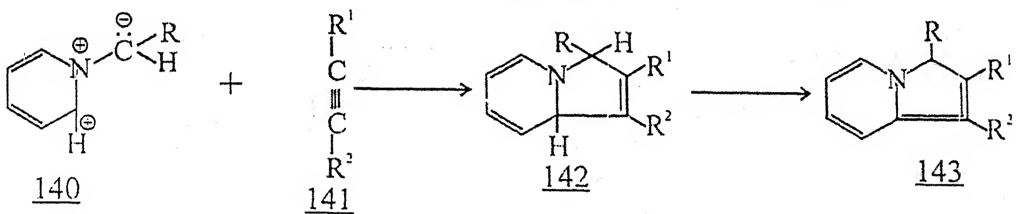
SCHEME IA.49



SCHEME IA.50



SCHEME IA.51



because of the remaining negative charge on the ylide carbon.[103] Previously it has been reported[104] that in disubstituted ylides, the negative charge of the ylide carbon atom is delocalized on the substituents but according to theroe - tical calculations, some negative charge remains on the atom.[105] This explains which ylidic compounds give (3+2) type of cycloadditions.

The pyridinium methylides (148) react with DMAD and lead to the formation of indolizines (150) by the loss of a hydrogen and an ylide substituent from intermediate (149) (Scheme IA.53). Isoquinolinium-methylides (151) also react [106,107] with acetylenic derivatives giving indolizine derivatives (154) dihydroindolizines 152 and 153 are the isolable reaction intermediates (Scheme I. 54). The quinolinium ylide (155), generated *'in situ'*, on reaction with DAMD in the presence of sodium hydride gives (3+2) cycloadduct (156)[108] (Scheme IA.55).

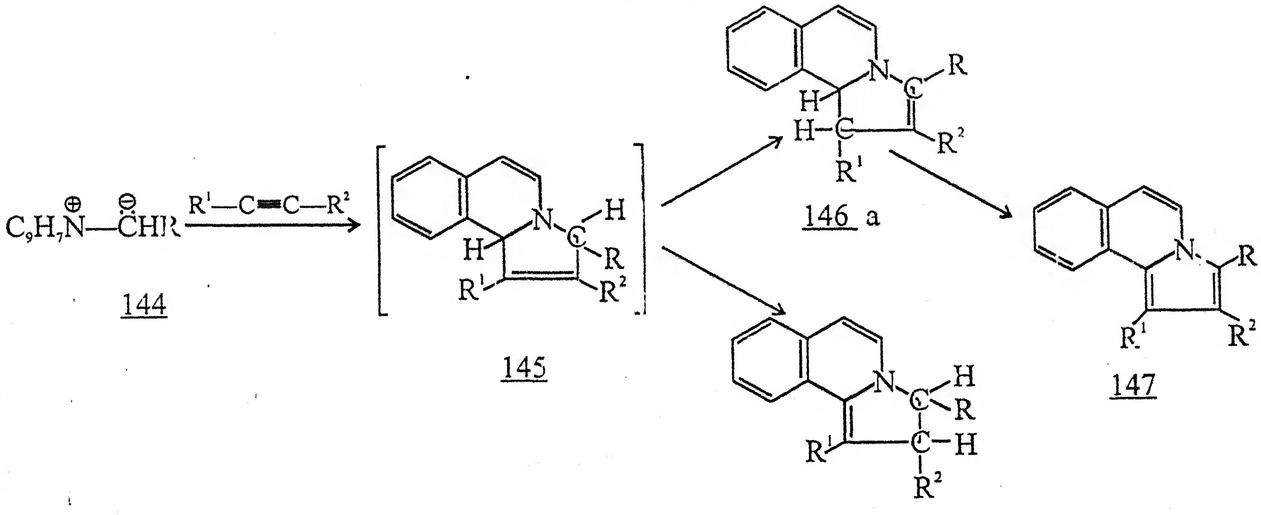
(c) Reaction with ethylenic compunds -

Mono and dicarbethoxyisoquinoliniummethylides (157 & 159) react with olefins in the presence of methanol, leading to the formation of tetrahydroindolizines[109] (160) with the elimination of an alkyl carbonate molecule from the intermediate (158) (Scheme IA.56).

(iii) (5+2) Dipolar Cycloaddition reactions

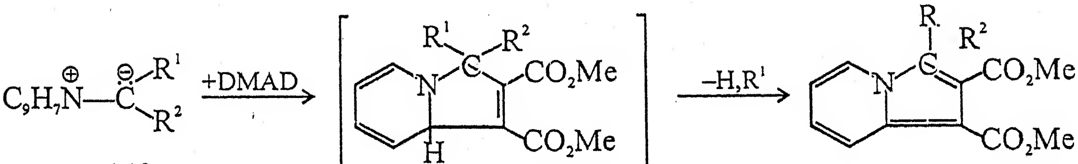
The charge distribution of highly electron withdrawing disubstituted ylide is such that they give a 1,5-dipole system (161). Zugravescu et al.[109,110] have isolated oxazepinic derivatives (162) during the reaction of

SCHEME IA.52



144 145 146 a 146 b 147

SCHEME IA.53



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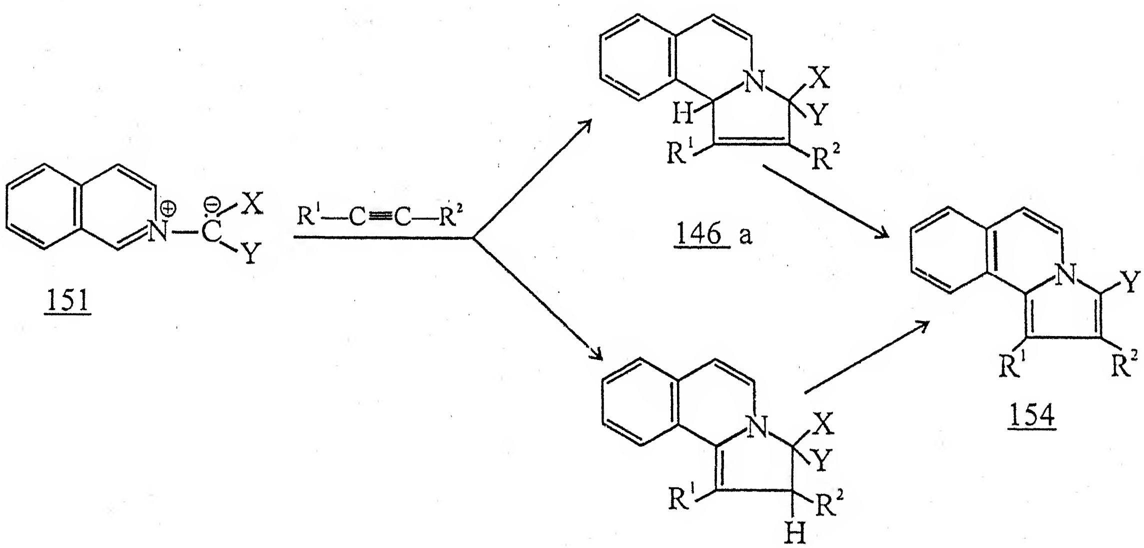


151 146 a 153 154

dicarbethoxyisoquinolinium methylides (161) with DMAD in benzene (Scheme IA.57).

(iv) (2+2) Dipolar cycloaddition reactions

Cyanocarbethoxy or carbmethoxy pyridinium ylides (163) react with DMAD in the presence of acetonitrile to give ylide (164)[111] (Scheme IA.58).

(v) Cycloaddition ivolving intermediate formation of an aziridine.

The dicarbmethoxyisoquinolinium-methylide (165), on its reaction with dicyanoacetylene or DMAD, afford the product (166) in very low yield. The formation of (168a-b) from the aziridine intermediate (167)[112-114] is the main part of the reaction (Scheme IA.59).

A.2.17 Metallation Reactions of Cycloimmonium Ylides.

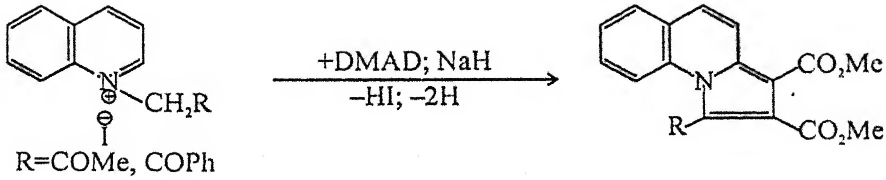
Pyridinium ylides, a class of cycloimmonium ylides, being the versatile ligands for metals in their various oxidation states, coordinate with metal ions as neutral ligands to form a σ-bond between the ylide carbon and the metal atom and thus lead to the formation of ylide-metal complexes.[115]

The mode of reaction and the formation of complexes depend upon the reaction conditions (solvent and reagents). For example, pyridiniumphenacylide on its reaction with various metal halides affords ylide metal complexes (169) (Scheme IA.60).

A.2.18 Some Spectral Properties of Pyridinium Ylides.

Krohnke and Bohlmann[116] classified as C-betaines, the ylides having maxima at 440-460 mμ and as O-betaines those with maxima 300-330 mμ. They concluded that the O-betaines included pyridinium bibenzoylmethylide

SCHEME IA.55



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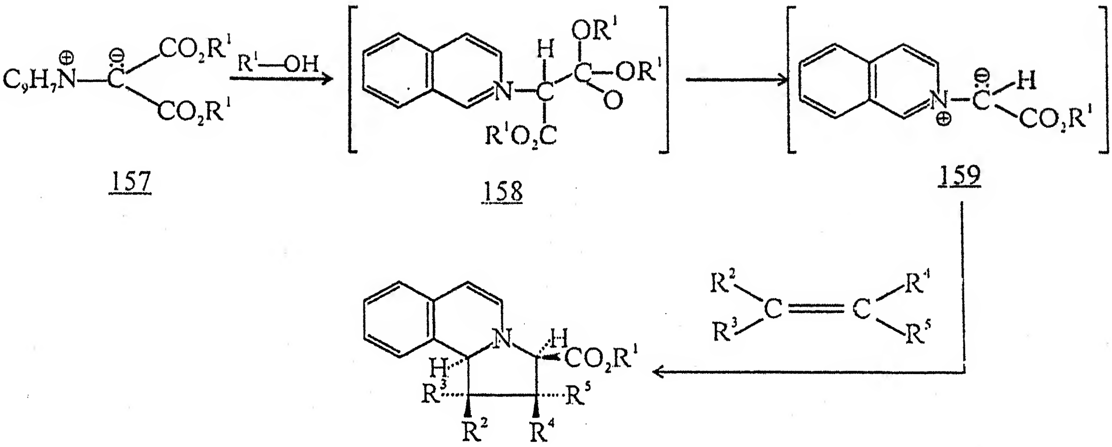
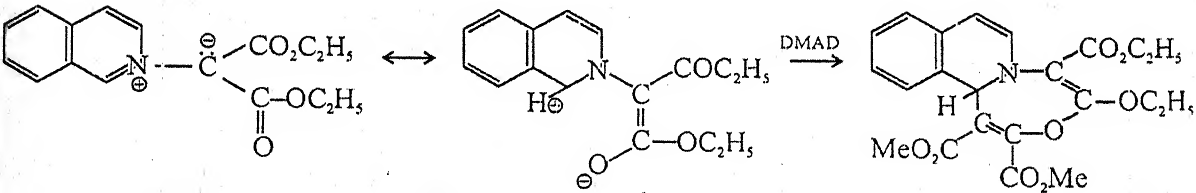


157 158 159

160

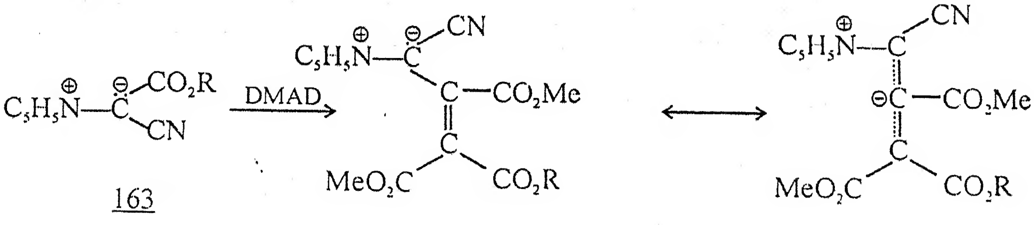
SCHEME IA.57



a 161 b

162

SCHEME I.58



163

164

and the C-betaines included all phenacylides. The spectra of pyridinium cyclopentadienylide in several solvents have been studied.[117]

Similarly, the visible absorption band of pyridinium ylide is attributed to an intramolecular charge-transfer transition (Scheme IA.61).

(a) IR Spectra

IR spectra of the ylides have been measured in chloroform solution. The spectra are complex but also show strong ylide carbonyl absorption[118-122] at low frequency. Thus, the ylide (170) (R=R'=Ph) absorbs near 1490cm^{-1} and the ylide (171) (R=Ph) near 1500cm^{-1}. This presumably indicates the structure (172) makes notable contribution to the resonance hybrids.

The ylides (173) and (174) absorbed strongly at 2166 cm^{-1} and 2185 cm^{-1} respectively which clearly indicates that structure (174 & 175) respectively contribute to the resonance hybrids.

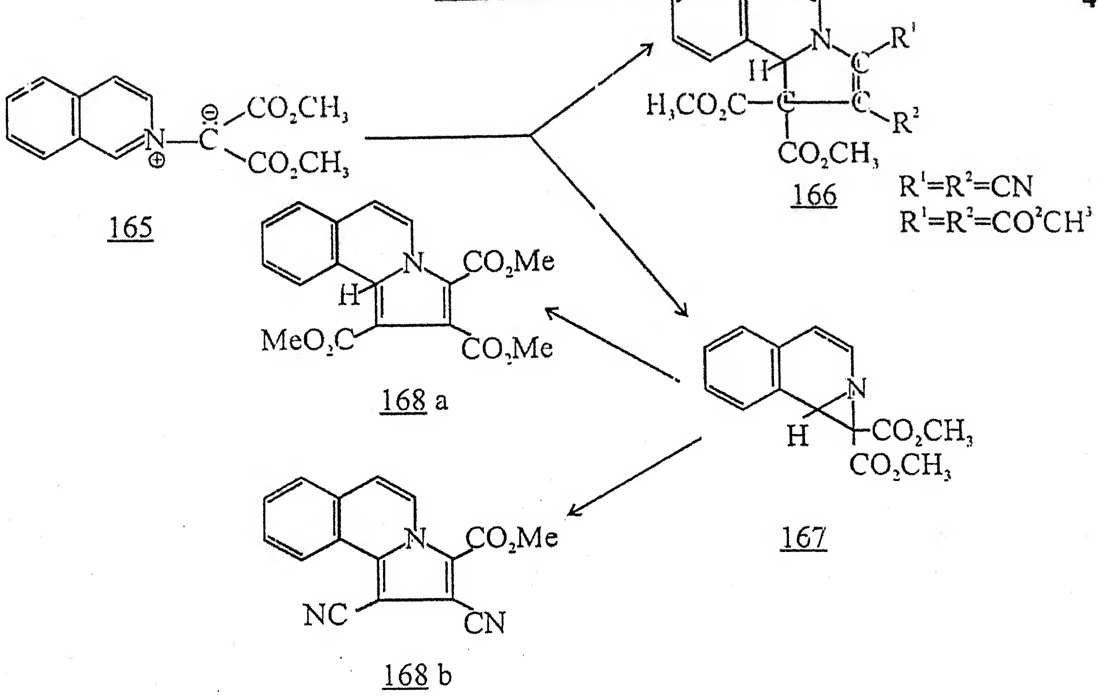
(b) NMR Spectra

The most interesting feature of the NMR spectra of the pyridinium ylides is the variation in the chemical shift of α-proton of the pyridine ring. In the perchlorate salt of 177 these protons absorb at δ9.21 (d_6-dimethylsulfoxide) but at δ8.63 (deutero chloroform) in the corresponding ylide:

$$\underset{\displaystyle Py^+}{EtOOC-\underset{|}{C}H-COOEt} \quad ClO_4^-$$

Similar values were observed for α-protons in the ylide (170) (R=Me, R'=Ph) and (172) (R=R'=Ph). This shift is to be expected because of the overall increase in electron density. However, in the cyano-ylides (173) and

SCHEME IA.59

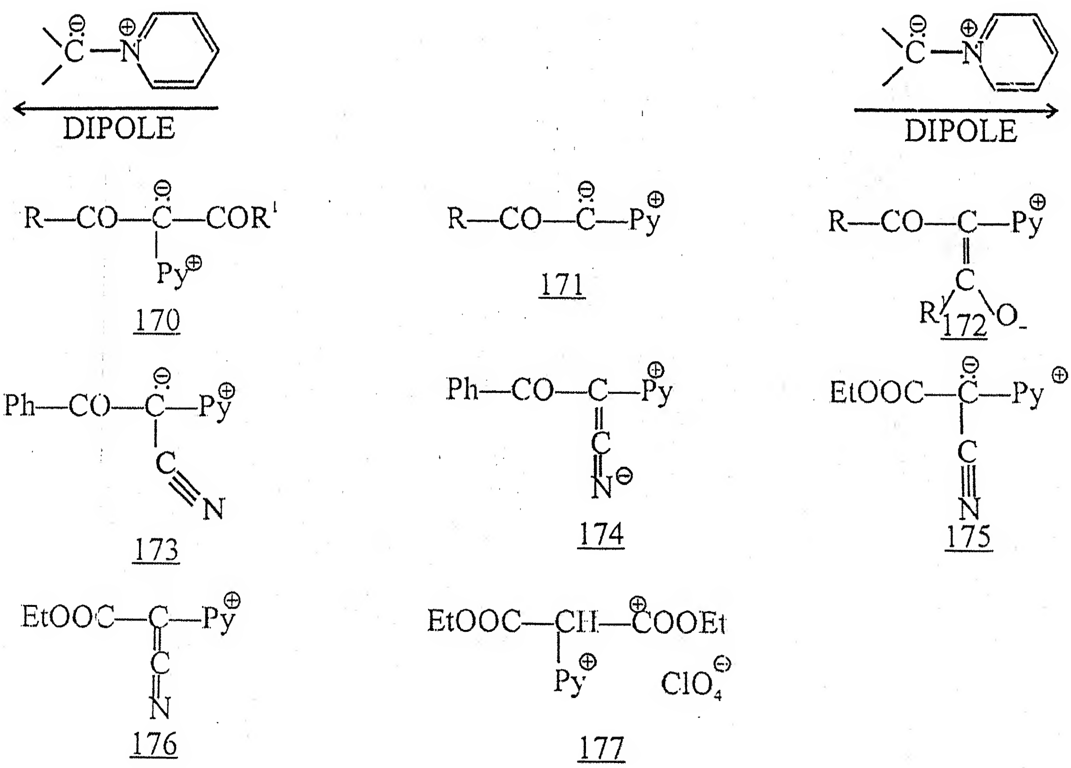


SCHEME IA.60

$$C_5H_5\overset{\oplus}{N}—\overset{\ominus}{C}HCOC_6H_5 + HgCl_2 \longrightarrow Hg_2\ [C_5H_5N—CH.COC_6H_5]_2\ Cl_4$$

169

SCHEME IA.61



(175), the α-proton absorbed well downfield at δ9.23 and δ9.31 respectively but the β– and γ-protons are not deshielded. This effect may also be explicable in terms of contribution of the structures (174) and (176).

1.2.19 Some Important Physical Properties of Cycloimmonium Ylides.

Surpateanu and Rucinschi[123] have shown that some isoquinolinium ylides are highly sensitive acid-base indicator which works on basis of the reversibility of the conversion reaction of deeply coloured ylide to be colourless quaternary isoquinolinium salts.

Surpateanu et al.[124,125] have also studied the semiconducting properties of some isoquinolinium ylides. The electrical conductivity of organic semiconductors is expressed by the equation :

$$\sigma=\sigma_0\, e^{-(Et/kT)}$$

where σ is the electrical conductivity corresponding to the absolute temperature T at which measurement was performed. σ_0 is electrical conductivity for $T\rightarrow\infty$, k is Boltzmann's constant, E_t is so called thermal activation energy.[126] The dependence of the electrical conductivity upon temperature for ylidic compounds proves the semiconducting character.

I.B Sulphonium Ylides (π-Sulpuranes)

Ylides (1) are a new and unique class of zwitterionic compund in which carbanion is covalently linked to a positively charged heteroatom. Its structure is considered as a resonance hybrid of two limiting structures: ylide form (1a) and ylene form (1b). One of

these, the ylide form (1a) emphasizes the dipolar zwitterionic nature involving an onium centre at elements like nitrogen, phosphorus or arsenic, next to a carbanionic function which may atleast be partially delocalized into suitable substituents. In the ylene form (1b), on the other hand, a true double bond is postulated between the centre and ylidic carbon, thus reducing or even eliminating the formal charges at these atoms[1-2]. The application of modern physical techqniques and the results of sophisticated theoretical calculation[3-5] have made it increasingly clear that the ylide form predominates in the ground state. Most of the early investigations successfully used in description for most of their problems of structure and reactivity and for the rationalization of reaction mechanism[2-6]. Therefore, it is with justification that the term ylide is used now a days almost exclusively in the literature.

The reactivity of the ylides depends both upon the properties of the carbanion and on the possible involvement of the heteroatom. These compounds vary widely in stability depending upon the symmetry of the molecule and the extent of p_π-d_π bonding.

A quantitative comparison of the stability of ylides formed by diffrent elements, have been made using the rates of alkali catalyzed exchange of the hydrogen atoms of the corresponding salts. The acidity of salt and hence the stability of the ylide is greatly affected

by the change in structure.

Ylide have been classified in two main groups on the basis of stability and ease with which they undergo reaction with a variety of electrophilic substrates. The first and the larger group comprises of ylides, called "non stabilized ylides" which are generated in the solution from their corresponding salts but could not be isolated due to lack of the stabilizing factors and undergo reaction in *situ*. These ylides may further be subdivided into two catagories depending upon the attachment of alkyl or arylalkyl groups with heteroatom. The arylalkylidene ylides, sometimes designated as semistabilized ylides could not be isolated but persisted in solution for a considerable time in contrast to the alkylidene ylides which are very short-lived. The second and the smaller group consists of "stabilized ylides" and is taken to imply an ylide which can be isolated, purified, usually stored in atmosphere and used in subsequent reactions. The stability of these ylides is attributed to the attachment of the electron withdrawing groups with the ylidic carbanion. In the recent years, the synthetic potentialities of ylides have been realized and studies on these reactive intermediates have been expanded in many directions which have led to the exploration of the ylides of nitrogen, phosphorus, arsenic and sulfur as evidenced by the research monographs[6-11] and comprehensive review articles[12-17, 126-134]. The involvement of a particular heteroatom

results into marked difference in the chemical and physical behaviour of different types of ylides.

The scope and potential for synthetic applications of these ylides have only recently been realized. Consequently, studies on pyridinium, phosphonium, arsonium and sulfonium ylides and their corresponding precursors have been very extensive. These investigations have led to the synthesis of a wide variety of heterocyclic compounds, vitamins, hormones etc, as evidenced by a large number of monographs[6-11] and comprehensive review articles[12-17]. A brief description under separate heads has been reviewed in the following section.

Ingold and Jessop's earlier investigations[135] gave the synthetic chemistry of S-ylides in 1930. His success was the isolation of a stabilized π-sulfuranes, a fluorenylidenedimethylsulfuranes (3) by reactivity 9-fluorenyldimethylsulfonium bromide (2) with aquous Na_2CO_3 (Scheme IB.1). This reactivity and synthetic potentialities in the literature is shown as isolated event. But in the early sixsteen a flury of activitites when G. Wittig[136] isolated successfully and studied the reactivitiy of P-ylides towards carbonyl compounds. It was his concluding fact that any molecular system capable of providing adequate stabilization to a carbanion may form an ylide[137] system and prompted from Wittig investigation in the P-ylide chemistry an active interest received by Johnson and Lacount[138] when they isolated fluorenylidene dimethylsulfurane (3) successfully. Reactivity of same ylide (3) having

the fact that the ylide afforded sufficient stabilization due to delocalisation of the lone pair of electron present on the ylide carbanion as shown by resonating structures (3a,b,c) and therefore prevented the ylide (3) from being entered into reaction of electrophilic substrate could not be studied too by them. With benzaldehyde the reaction of ylide (3) form, a benzalfluorene was failed becasue it provided benzalfluorene oxide (5) and phenyl-9-(methythamethyl) flourenyl carbinols (6) in place of benzalfluorence (Scheme IB.2).

In connection with the same Corey and Chaykovsky[139] reported reactions of the preparation more reactive and a less stable ylide methylenedimethyloxosulfonium ylide (7). Having the ability of P-ylides to act as a good carbonyl olefinating reagent[126,] Corey et al[140] have also tried to react oxosulfonium ylide (7) with aldehydes and ketones (8) and assumed to get the olefins but failed because of the exclusive products were epoxides (9) (Scheme IB.3).

In accordance with these observations oxosulfonium ylides were known as a versatile status of epoxidation reagents. Now these exclusive methods were made to explore the synthetic potentialities of these ylides[140].

After this, Franzen and Driessen[141] made a successful attempt to synthesize a new kind of sulfuranes also called sulfonium ylides (12) through the interaction of methylphenyl sulfide (10) with methyl

1a 1b

(where X may be N, P, As, S etc.)

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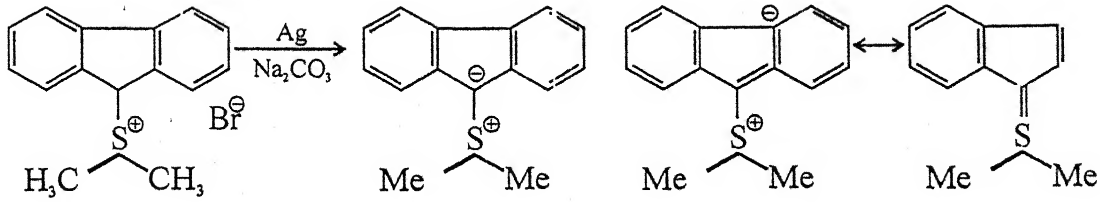
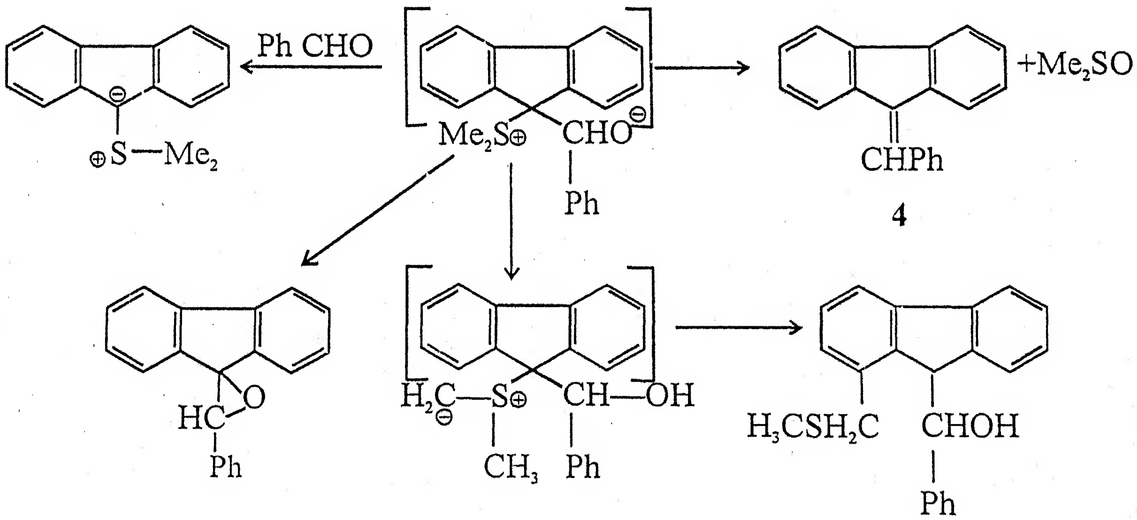


2 3a 3b 3c

SCHEME 1B.2



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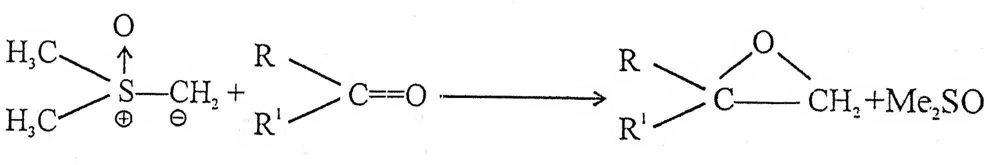
SCHEME 1B.3



7 8 9

iodlde (11) followed by dehydrohalogenation (Scheme IB.4). In comparison to oxosulfonium ylide (7), the ylide (12) so formed was less stable. This has been represented by the fact that the ylide gets decomposed in the absence of suitable substrates.

In the subsequent years Corey and Chaykovsky[142] have reported that sulfonium ylides undergo not only methylene transfer reaction on carbonyl group to form epoxides but also add on C=C having some unsaturated groups in conjugatified itself as appropriate epoxidation reagent to provide oxirane (13). Oxosulfonium methylide has capabilities to add on to activated C=C to form cyclopropanes (14). Thus undoubtlly sulfuranes are the best methylene transfer agents[143] (scheme IB.5). Incoming years, the synthetic potentialities of sulfuranes have further been realized and illustrated in many ways with a view to test the domain of the applicability of these ylide systems as evidenced by recent monographs and several comprehensive review articles[144-150].

A type of classes of π-sulfuranes are known the most common being sulfonium ylides (15), oxosulfonium ylide (16), sulfenyl ylides (17), sulfinyl ylides (18) and imino sulfuranes (19).

The stability of π-sulfurance may be attributed to the electrostatic stabilization as well as delocalization of charge on the ylidic carbanion with d-orbitale of S-atom[151-152]. The magnitude of electrolytic stabilization of π-sulfuranes is completly controlled by the magnitude

of charges present on the onium group as well as on the carbonion of ylide Illustrating to this fact it can be observed that oxosulfonium ylides are more stable than their sulfonium counter parts, having to the increased positive charge on the S atom due to the presence of more electronegative oxygen atom. Another factor which also makes a notable contribution to the stability of π-sulfuranes (20), is delocalization involving the use of 3d orbitals which is the maximum. If the sulfur atom carries a full unit of (+) ve charge, the overlapping of doubly occupied 2p orbital of the ylide carbon with the formation of π-bond while the lone pair on S remains in a 3p orbital. This can be represented in the resonance hybrid of two limiting structures, the ylide form (20a) and the ylene form (20b). These factors are sufficient enough to explain as to why a series of π-sulfuranes have been isolated and charecterized as stable species. Further more, the maximum overlap of a 2p carbon orbital (21a) with a 3d orbital of S-atom is reported only when the molecule had the tendency to become coplaner (21b) and can be represented by p_{π}-d_{π} orbital overlap structure (21).

However, from recent ESCA data it has been concluded that the stability of these ylides is also influenced by the presence of certain electronegative groups on the ylide carbon. The reason is that the formal (–)ve charge on the ylide carbon actually, highly delocalization into substituents attached to the ylide carbon (22).

The reactivity of π-sulfuranes depends on the properties of the carbanion as well as the possible involvment of the heteroatom[142,153-162]. Usually alkylidenesulfuranes of less stability show high reactivity whereas highly stabilized alkylidenesulfuranes show less reactivity. The reactivity of alkylidene sulfuranes is influenced by the distribution of the (-) ve charge over the molecule which, in turn, depends on the nature of the substituents R^1 and R^2 in the alkylidene position as well on the group R on sulfur. Thus, the nucleophilic charecter of the sulfurane decreases if the lone pair of electron on the α-carbon atom of the form (20a) is delocalized into group R^1 and R^2 tend to stabilize the (-)ve charge and consequently reduce the reactivity of the ylides. On the other hand, when there is no such interaction, an extremly reactive and unstable π-sulfurane is formed.

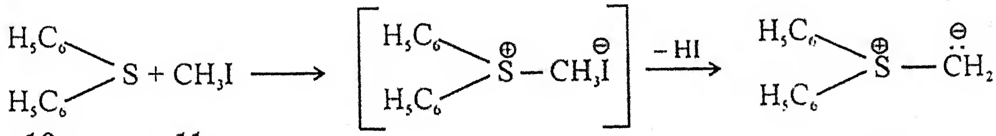
Prompted from the enhanced reactivity and easy preparation of the π-sulfuranes, it was thought to be of interest to focus our attention on synthesizing some new sulfonium ylides with a view to test their reactivity towards a variety of electrophilic substrates resulting into the formation of diverese carbocyclic and heterocyclic systems[163-166].

IB.1. Preparation of π-sulfuranes Viz. Sulfonium ylides

IB.1.1.π –Sulfuranes (sulfonium ylides) from sulfonium salt

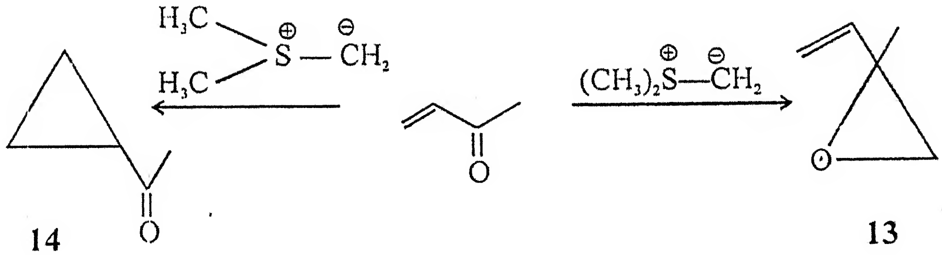
This remains the most common method of generating π–sulfuranes and involves the reactions of sulfonium salt with a base

SCHEME 1B.4



10 11 12

SCHEME IB.5



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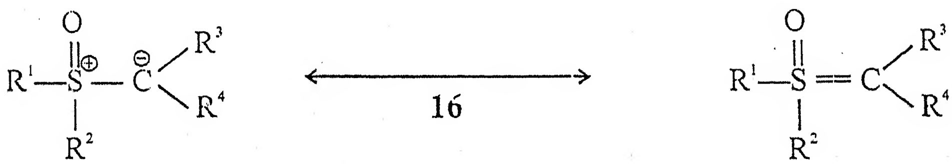

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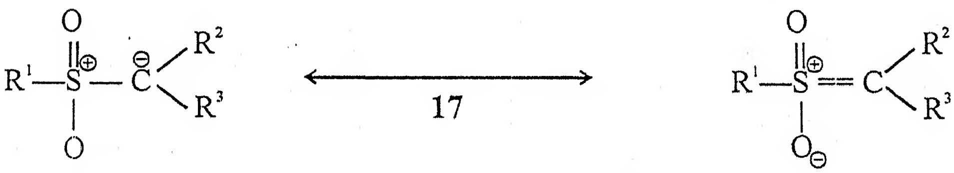

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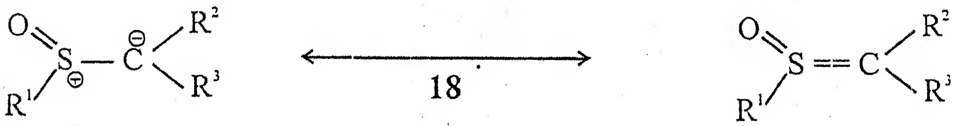

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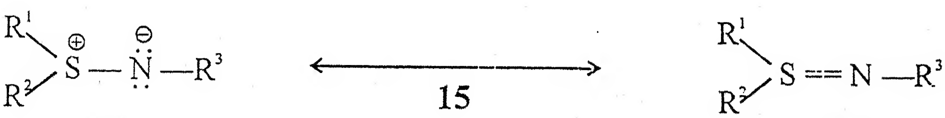


15

20a 20b

which is strong enough to abstract proton from α-carbon. In principle, any sulfonium salt (23) carrying at least one α-hydrogen is convertible into an ylide (24) (scheme IB.6). In practice, the salt method is applicable only to these structural situations. In the first instance, all the three of the groups attached to the S atom must be identical so that it makes no difference which α-hydrogen is removed by the base. In the second instance one or two of the substituents have no α-hydrogen but these groups which are identical[141]. The first and the last structural situation in which the sulfonium salt method[135-163] is applicable and necessitable there is an appreciable difference in the acidity of various available α-hydrogens and the availability of a base of the proper strength. The deprotonation of the more acidic α-hydrogen is always preferred. If α-hydrogen and each of approximately the same acidity, a mixture of π-sulfuraes result (Scheme IB.7).

Numerous bases have been employed for the generation of sulfuranes and the sterngth of base to be used depends on the acidity of the sulfonium salts. Thus, trialkylsulfonium salts required very strong bases such as methyllithum[164], potassium-t-butoxide[138,165] in dimethylsulfoxide or methylsulphinyl carbanion[141-142], Further literature survey revealed that in the generation of stabilized sulfuranes only relatively weak bases such as trimethylamine aq NH_3 or aq. NaOH[57] are respectively required. Also solvents such as dimethylsulfoxide or tetrahydrofurane are reported to be used for the non stabilized π-

sulfuranes[167]. Protic organic solvents or water have been shown to react with the non stabilized π-sulfuranes and therefore these solvents have not been employed for their generation[168-170] of π-sulfuranes.

IB.1.2. π-sulfuranes from benzyene and organic sulfides

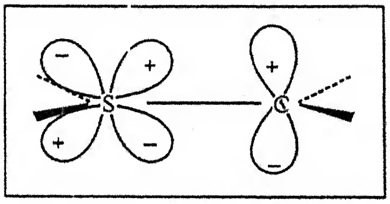
Among few othor methods[171-174] employed for the generation of sulfuranes are involving the react on of dialkyl sulfides (29) with benzyne (30) used for generation of such - sulfuranes (ylides) (31) in which S-atom of the ylide carried one phenyl ring[175]. But in practice, this method is of little importance. Because the presence of phenyl ring in resulting ylide renders them less reactive due to delocalization of the (+) charge carried by S-atom phenyl ring (scheme IB.8)

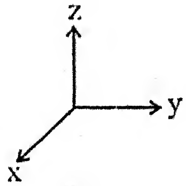
I.B.3 π-sulfuranes via alkylation and acylation method

A wide variety of complex which are quite inaccessible by the conventional salt method have been prepared by the method called alkylation[176] or acylation[177]. The method involves the interaction of the simple ylides with alkylating or acylating reagent to form more substituted stabilized ylides (scheme IB.9).

IB.1.4. π-sulfuranes from active methylene compound and sulfoxides

The condensation of active methylene group (33) with sulfoxides or alkoxysulfonium salts (32) offers a direct route for the synthesis of highly stabilized ylide (34) via intermediate salt formation[178-180] (scheme IB.10).





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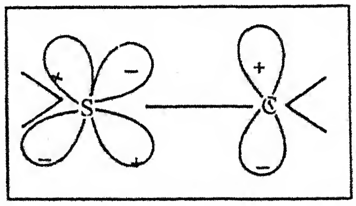
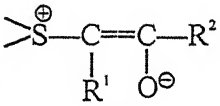


yz plane

21a

xy plane

21b



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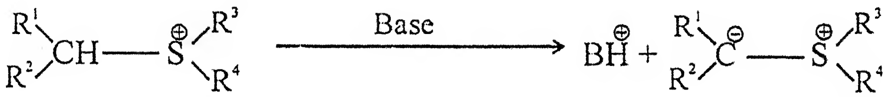
SCHEME IB.6



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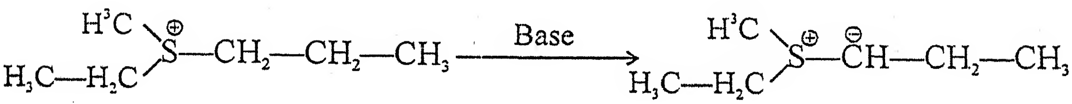
SCHEME IB.7



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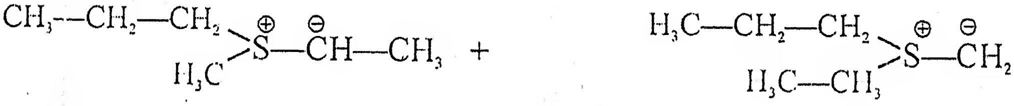

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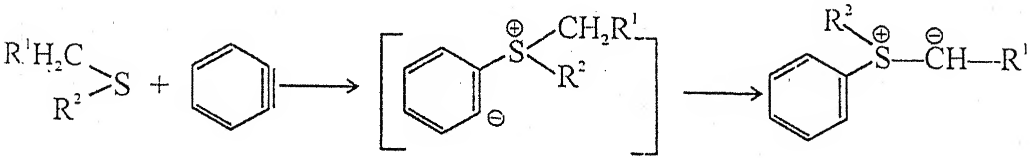
SCHEME IB.8



29 30 31

The reaction with sulfoxides is favoured in presence of dehdrating agents.In general acetic anhydride, phosphorus penoxide, phenylisocyanate and dicyclohexyl carbodi-imidophosphoratic acid are highly suitable for bringing about the desired results.

IB.1.5 π-Sulfurance from carbenes

The addition of carbene to a sulfide provides a most direct synthesis of π-sulfurance (Scheme IB.11)[181-183] Diazo compounds serve as a good source of carbene intermediate for the preparation of ylides (37). The copper catalyzed thermal or photolytic decomposition of diazo compounds (36) in presence of an allyl benzyl sulfide (35) appears to be the most attractive synthetic technique (Scheme IB.12). However, it was observed that thermal decomposition of diazo compounds is more suitable for synthesizing ylides.

IB.1.6 π-Sulfuranes via Michael addition to vinyl sulfonium salt

The Michael addition to a vinyl sulfonium salt (38) also produces π-sulfurances[184-185] (Scheme IB.13). The resulting ylide (39), if stable, is isolable and can be trapped by the attack of suitable reagents or it can further react intermolecularly.

IB.1.7 π-Sulfurane from electrochemical reduction of sulfonium salts

Only one example relating to the prepration of ylide (41) by

this method is given in the literature[186] which involves the reduction of trimethylsulfonium salt (40) in DMSO solution (Scheme IB.14).

IB.1.8 π-Sulfuranes from other methods:

Dimethylsulfoniummethylide is capable of being prepared in good yields by the phase transfer catalysis[187]. A ligand exchange reaction between triphenylsulfonium cation and cyclopropyllithium gives diphenylsulfonium cyclopropylide[188] in good yields. The synthesis of thiaranes[189] and an asymmetric synthesis Thiaranes[190] by the reaction of aldehydes and ketones with s-lithiomethyl 1-0(-)methyl dithiocarbonate have been reported recently.

1B.2 Reaction of π-Sulfurance:

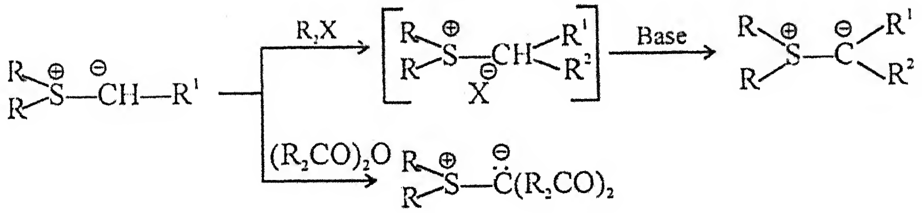
IB.2.1 Phenacyldimethylsulfonium bromide with hologen acids

Ratts et.al.[166] have reported that phenacylidene dimethyl sulphonium ylide on its reaction with HBr acid affords dimethyl-phenacylsulfonium bromide. Johnson et. al.[177] tested the reaction and demonstrated that almost all the carbonyl stabilized sulfonium[151] ylides react with hydrogen bromide (43) to form conjugate acid (44) of the ylide (42) (Scheme IB.15). These observations clearly indicate that sulfonium ylides are nothing but the conjugate bases of dimethylphenacylsulfonium bromide.

IB.2.2. Thermolysis of π-sulfurances

The existing literature lacks in sufficient information concerning the thermolysis of sulfonium ylides. However Johnson et.al[179] have

SCHEME IB.9



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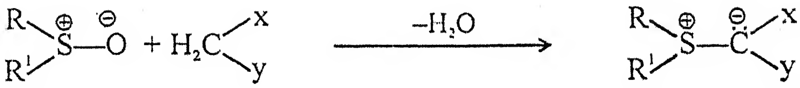

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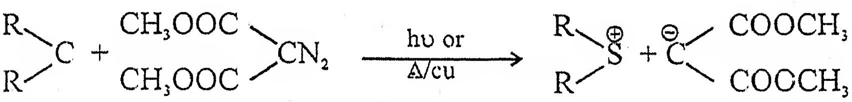
SCHEME IB.12



35 **36** **37**

SCHEME IB.13

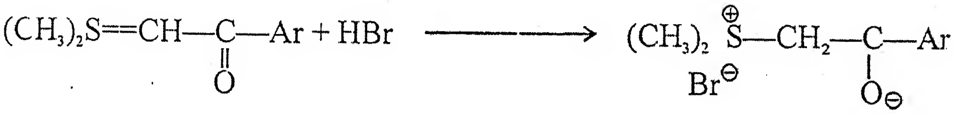
$$CH_2{=}CH{-}CH{=}CH\overset{\oplus}{S}(CH_3)_2 + NaOCH_3 \longrightarrow CH_3OCH_2CH{=}CH\ddot{C}H\overset{\oplus}{S}(CH_3)_2$$

38 **39**

SCHEME IB.14

$$(CH_3)_3\overset{\oplus}{S} \xrightarrow[DMSO]{e^{\ominus}} (CH_3)_3\,S^{\bullet} \xrightarrow{-H^{\bullet}} (CH_3)_2\,\overset{\oplus}{S}{-}\overset{\ominus}{C}H_2$$

SCHEME IB.15



shown that the non stabilized sulfonium ylide, diphenylsulfonium benzylide (45), on thermolysis dissociates into carbenes (46) and phenylsulfide (47) (Scheme IB.16). On the other hand, thermolysis of stabilized ylide, phenacylidenedimethylsulfurance (48) takes different course[191-192] where carbene generated by the thermal dissociation of the ylide dimerises to form dibenzoylethylene which, in turn, is attacked by one mole of the original ylide (48) affording 1,2,3-tribenzoyl-cyclopropane (49) through carbenoid mechanism (Scheme IB.17).

IB.2.3. Photolysis of π-sulfuranes

Photolytic conversion of the π-sulfurances have been less studied. However Trost et. al[193] have reported that photochemical decomposition of diphenyl sulfonium allylide (50) occurs in which cyclopropane (51) is isolated in 25% ylides (Scheme IB.18). Subsequent to this, corey and chaykvsky[194] developed an Arndt-Eistert type of process to yield esters (54) by irradiation of β-keto-oxosulfonium ylide (53) prepared by acylation of methylido (52) (Scheme IB.19).

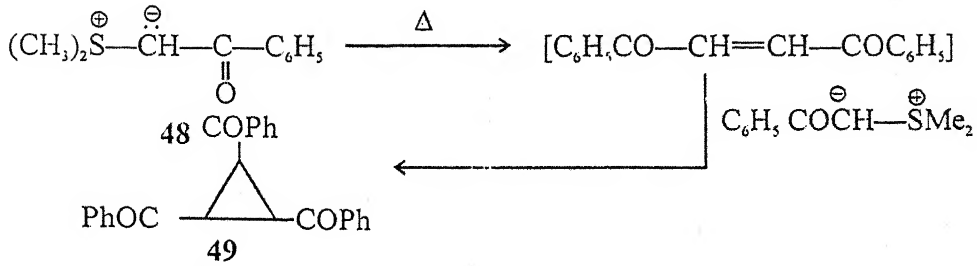
IB.2.4 Tribenzoyl cyclopropane (with α-bromo ketones)

Johnson et al[195] have reported that the phenacylidinedimethyl sulfurane (55) reacts either with its conjugated acid (56) or phenacyl boromide (57) to afford tribenzoyl cyclopropane (58). The mechanism of the reaction appears to involve an acylation via elimination addition

SCHEME IB.16

$$\underset{\mathbf{45}}{(C_6H_5)_2\overset{\oplus}{S}\text{—}\overset{\ominus}{C}HC_6H_5} \xrightarrow{\Delta} \underset{\mathbf{46}}{:CHC_6H_5} + \underset{\mathbf{47}}{(C_6H_5)_2S}$$

SCHEME IB.17



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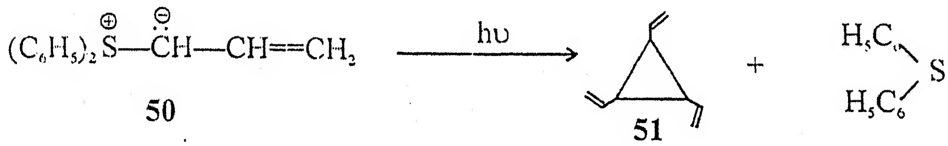

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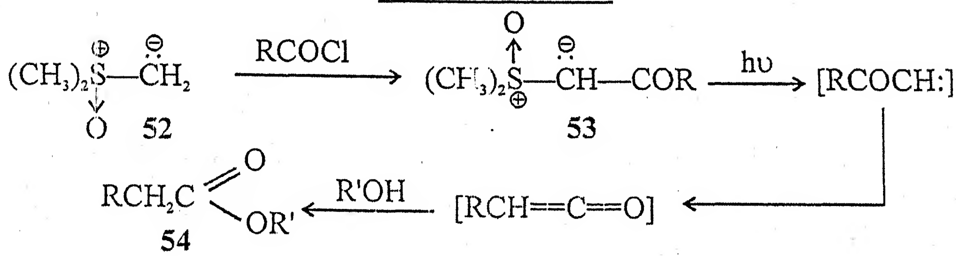

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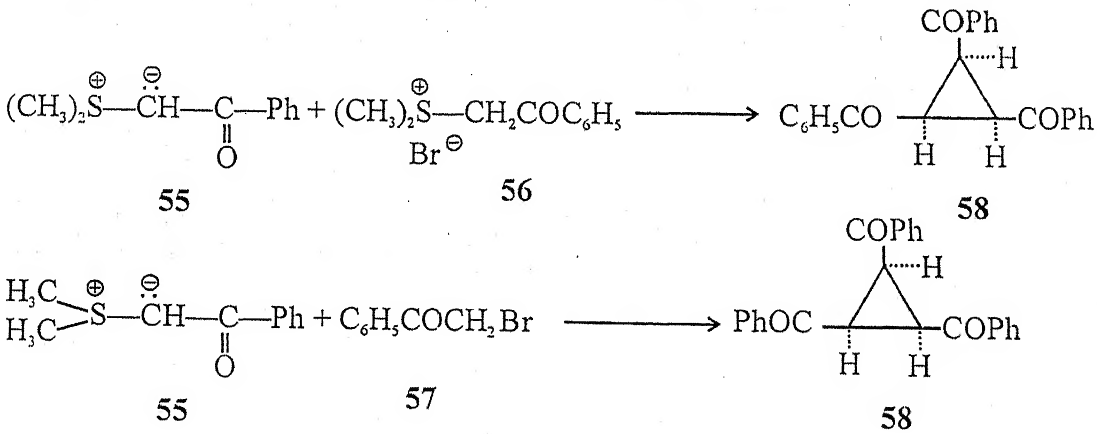


sequences (Scheme IB.20).

IB. 2.5. Alkylation of π-sulfurances

The alkylation reactions have assumed importance because of their ability to offer a versatile route for synthesis of disubstituted ylides which are otherwise difficult to prepare. Other route Johnson et al[177] studied the alkylation of phenacylidine dimethyl sulfurane (59) with benzyl bromide (60) where α-methyl-thio-β phenyl propiophenone (61) was reported to have been formed (Scheme IB.21).

IB.2.6 Acylation of π-sulfuranes

Based on information gathered so far non stabilized π-sulfurances are not liable to be attacked by acylating reagents. However stabilized π-sulfurane are reported to undergo acylation reaction with a couple of acylating reagents[177,196] and it is observed that the course of acylation depends on the nature of the acylating reagents. Thus phenacylidenedimethylsulfurance (62) on reaction with benzoic anhydride undergoes C-alkylation to afford a new ylide (63). On the other hand ylide (62) follows O-acylation when treated with benzoyl chloride, thus affording enol benzoate (64) (Scheme IB.22).

IB.2.7 Synthesis of Indoles : Reaction of sulfonium ylide with Amino Compunds

Bravo and his coworkers[197] have synthesised a wide variety of substituted indoles (67) by the reaction of dimethylsulfoniummethylide

(65) with aromatic amino carbonyl compounds (66) (Scheme IB.23). Later on Junjappa[144] reported the formation of 2-substituted indoles (70) by the interaction of carbonyl stabilized sulfurane phenacyldene-dimethylsulfurane (68) and substituted anilins (69) in the presence of diethylaniline (Scheme IB.24).

IB.2.8. Synthesis of Benzothiophens : Reaction of sulfonium ylide with mercapto compound

Brave et al[198] have demonstrated that dimethylsulfonium methylide (72) is capable of undergoing reactions with o-mercapto ketones (71) forming benzothiophenes (73) (Scheme IB.25).

IB.2.9. Synthesis of pyrazole derivatives : Reaction of sulfonium ylide with nitrile amine

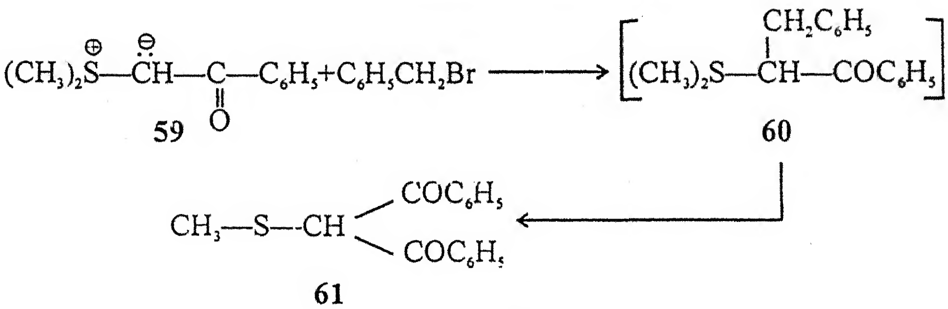
The carbonyl stabilized sulfonium ylides have also been reported in literature[199] to undergo reaction with nitriteamine affording pyrazole derivatives. For example, the reaction of stabilized π-sulfuranes (74) with N-(α-chlorobenzylidene) N-phenyl hydrazine (75) affords pyrazole (77) via intermediacy of the cyclic products (76). This reaction has assumed big importance in the synthesis of pyrazole derivatives (Scheme IB.26).

IB.2.10. With multiple bonds

2.10.1 With C=O double bonds

The best known reaction of sulfonium ylides which attained importance in the preprative organic chemistry under the name of

SCHEME IB.21



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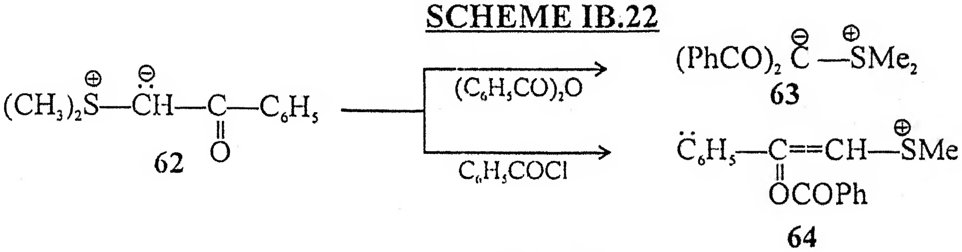
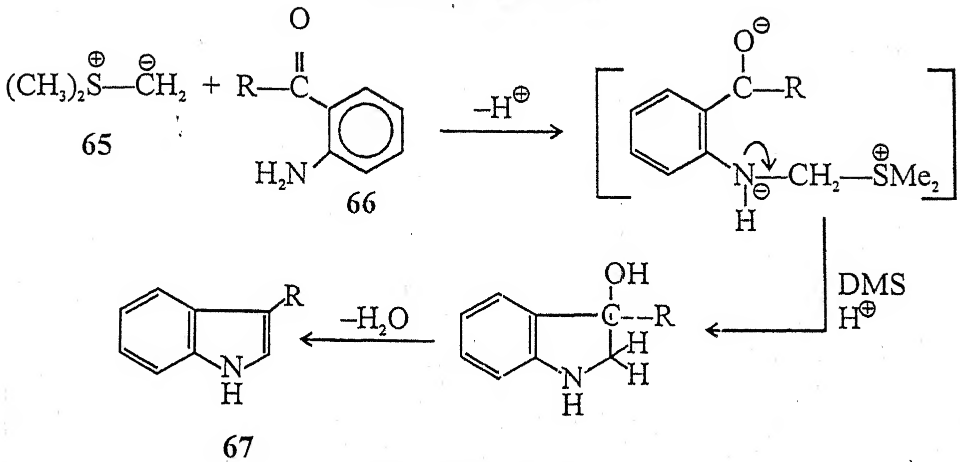


SCHEME IB.23



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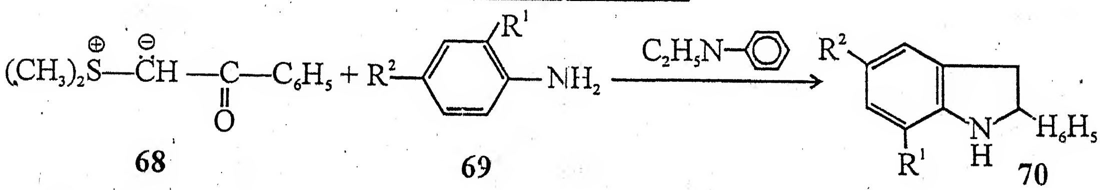
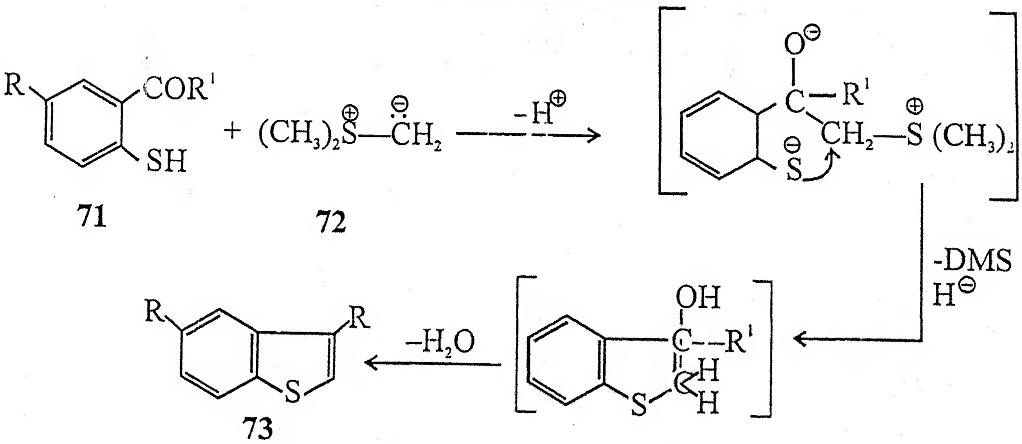


SCHEME IB.25



epoxidation involves the combination of these ylides (78) with carbonyl compounds (79) to form oxiranes (81) exclusively. The reaction proceed via the intermediacy of betaine type of compound (80) formed by the nucleophilic attack of the ylidic carbonion on the carbonyl carbon atom and involving displacement by the oxyanion on the carbon carrying the onium group. It appears in the case of sulfonium betaine (80) that the potential S-O bond formation is not a sufficient driving force to dictate the course of the reaction[200] (Scheme IB.27). The conjugation and stabilization afforded by the substituents (R^1) present on the ylide as well as on the carbonyl group (R^2,R^3) to an incipient double bond in the transition state appears to be the rate controlling factor.

In the absence of such stabilisation oxiranes formation may vary easily by the normal course of events as is observed in the case of methylides[201].

Non stabilized π-sulfuranes e.g. methylenedimethylsulfurance (82) when reacted with carbonyl compounds (83) such as benzaldehyde cyclohexanone and benzophenones afforded the epoxides (84) in fair to good yields (Scheme IB.28). In the year 1961, Franzen et al[56] further extended the reaction of these ylides with α , β -unsaturated ketones and have shown that the exclusive formation of epoxides and non isolability of cyclopropanes. In the subsequent years Johnson et al[169,202] took the credit of synthesizing substituted benzylidine diphenyl

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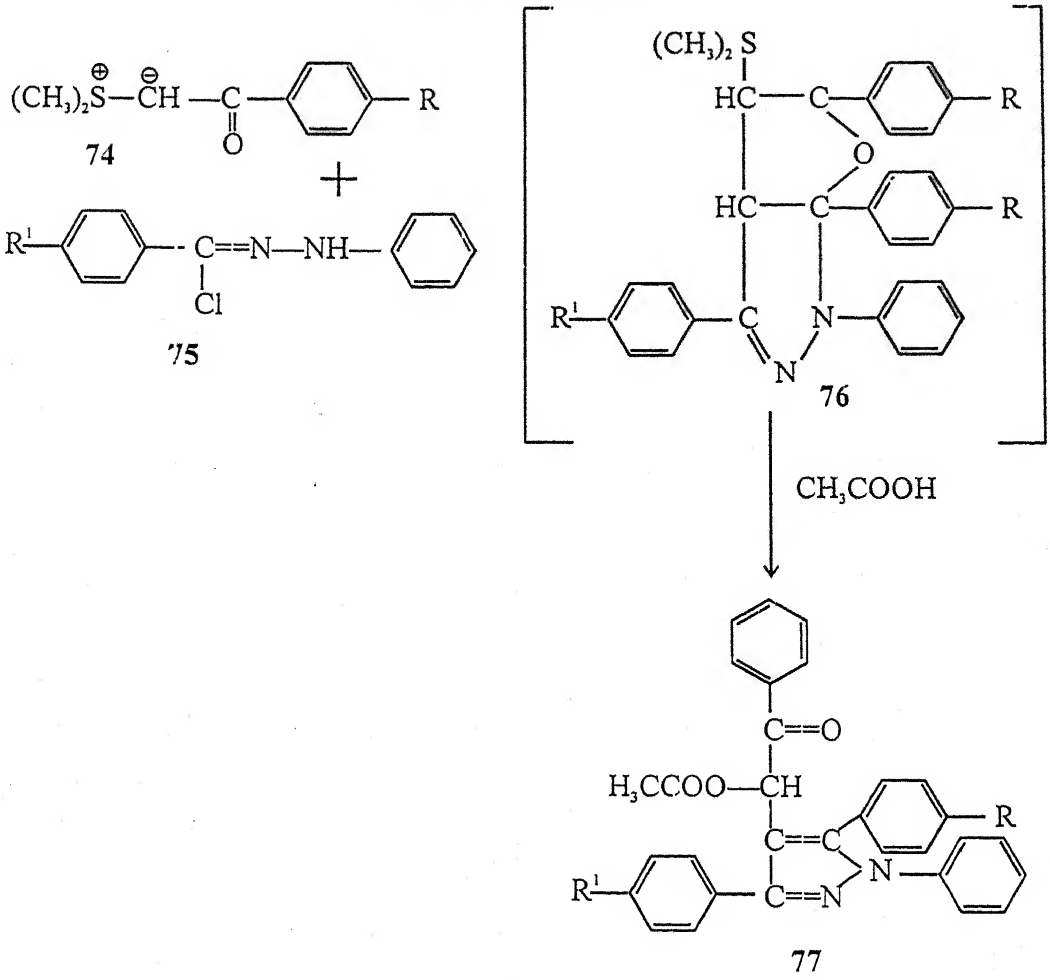
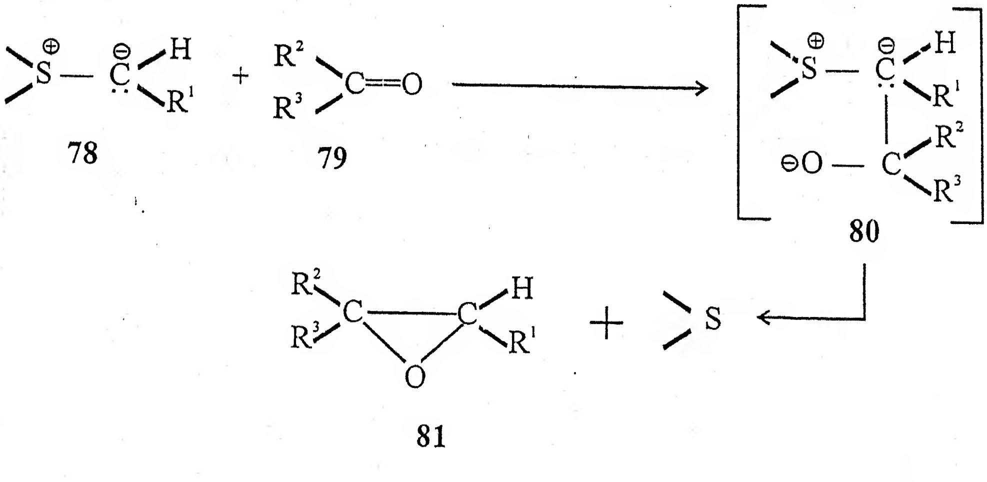


SCHEME IB.27



sulfuranes (85) and have studied their reaction with carbonyl compounds (80) which lead to the formation of epoxides (87) exclusively (Scheme IB.29). These studies revealed that in π-sulfurance unlike arsonium ylides[203], the course of the reaction with carbonyl compounds can not be attended by the nature of group present on the benzylic position of the ylide carbanion, as a result these ylides[204] have been succeessfully employed for the synthesis of nitro substituted stibenes oxides which are quite inaccessible by their arsonium counterparts owing to the fact that nitro group favours the reaction to proceed in the direction of olefines formation.

Unlike non stabilized π-sulfuranes which are quite reactive against carbonyl function giving epoxides exclusively. Stabilized π-sulfuranes[171] do not react with carbonyl functions. Non reactivity towards carbonyl function is due to the decrease in nucleophilicity of these ylides. However, Johnson and Lacount[138] were first to study the reaction between stabilized π-sulfuranes : fluorenylidenedimethyl sulfurane (88) and benzaldehyde (89). when epoxides (90) was found to be the exclusive product (Scheme IB.30). Thereafter Payme et al[205] have demonstrated that stabilized ylides could be made to react with such systems in which carbonyl group is in conjugation with the highly electroposotive group which enhances the electrophilic characters of carbonyl atom, thus making them to enter into reaction

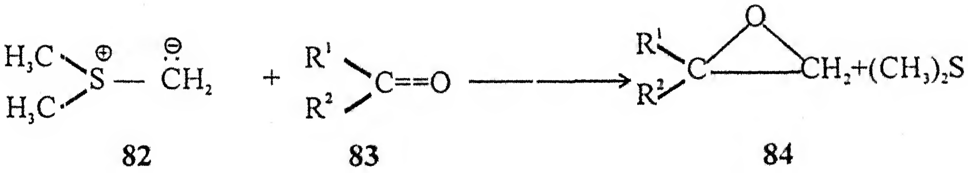
with the sulfonium ylides.

2B.10.2 With C=C double bonds : Synthesis of Cyclopropane

Prompted by the ability of π-sulfuranes to act as a versatile methylene transfer reagent as evidenced by the fact they form epoxides on their attack on carbonyl function, curiously aroused among the organic chemists to explore the reactivity of π-sulfuranes towards C=C. One of the first attempts in this direction came in the form of investigation carried out by Corey and Chaykovsky[139-142] which involved the nucleophilic addition of dimethyl oxosulfonium methylide (91) with chalcone (92) to produce trans-l-benzoyl-2-phenyl cyclopropane (93) (Scheme IB.31).

However cyclopropanation reacations starting from sulfonium salts (94) to form 1,2,3-tribenzoyl cyclopropane (97) were also known earlier[206], although, the reaction machanism of the reaction was not clear. Only in 1966 it was demonstrated[82-83] that the reaction proceeded by the addition of dimethylsulfonium phenacylidene (95) to dibenzoyl ethylene (96) (Scheme IB.32). However, the case with which cyclopropanation takes place depends on the nucleophilic character of the ylide carbanion. This can be illustrated by the fact that non-stabilized π-sulfuranes readily attack over C=C bond due to enhanced nucleophillicity by the absence of stabilization factors giving cyclopropane derivatives. On the other hand, it was observed that stabilized π-sulfuranes which are relatively less nucleophilic attack on

SCHEME IB.28



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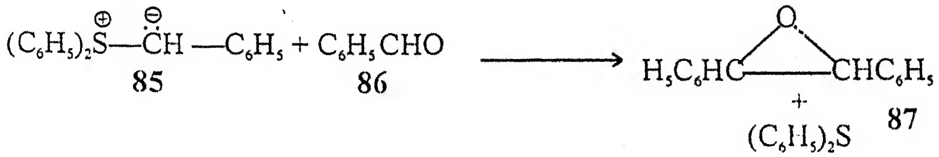
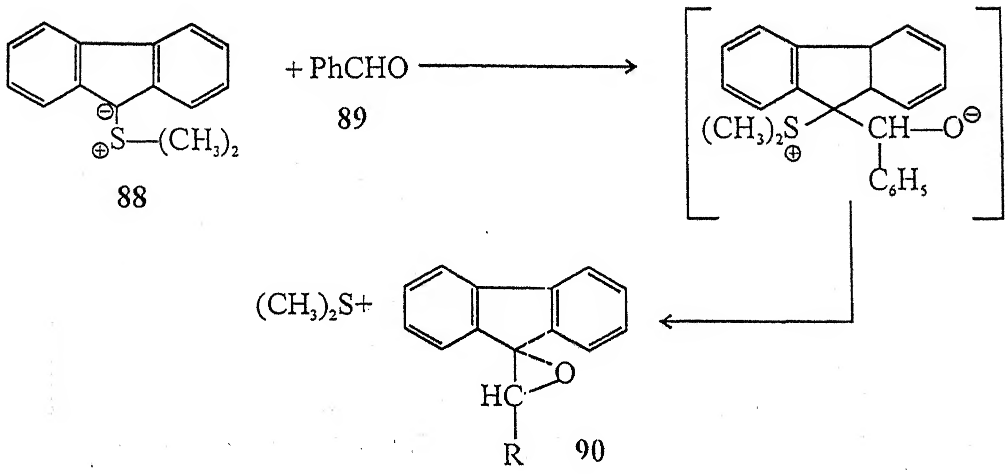


SCHEME IB.30



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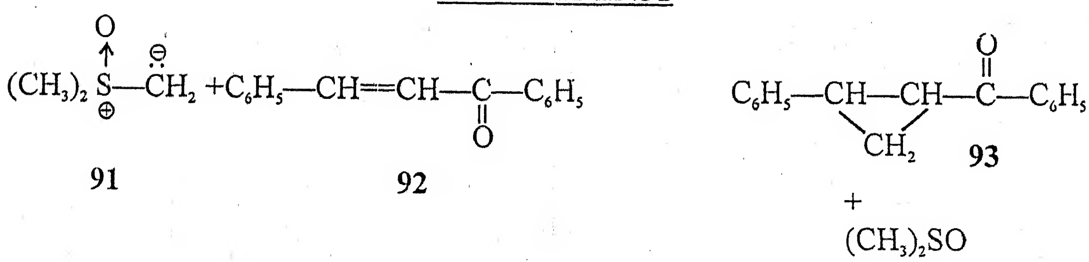

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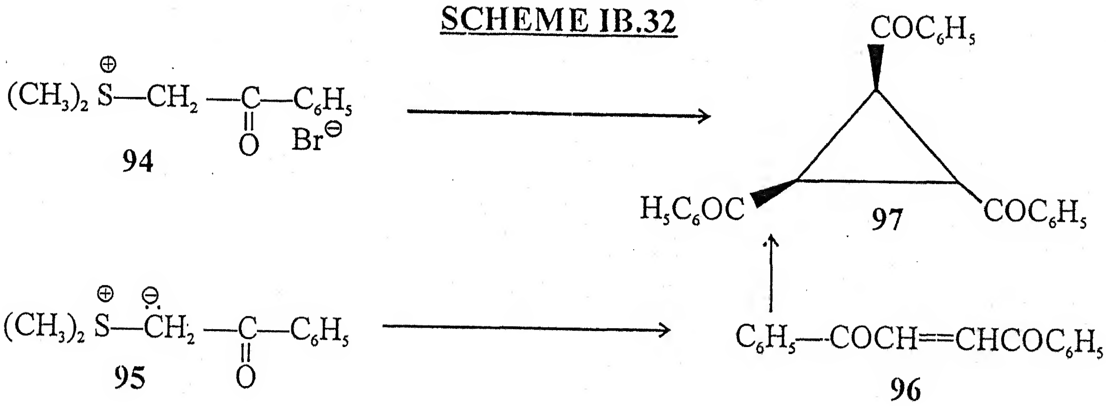


conjugated C=C system only.

Subsequent to these investigations the method of introducing cyclopropanes has become one of the most important in daily methods besides one involving carbene addition. Payme[207] has shown by studying the addition of carbethoxydimethyl-π-sulfuranes (98) to the hexanone (99) that the nucleophilic methylene transfer takes place at the double bond to form cyclopropane (100) and not on carbonyl group (Scheme IB.33). In this way cyclopropanated steroids[208] and nucleosides[209-210] have been synthesised.

2.10.3 With C-N double bond : Synthesis of Aziridines

Franzen[141] and Corey[142] have studied the reaction of non stabilized π-sulfurances : methylene dimethyl sulfurane (101) with schiff's bases (102) leading to the formation of a variety of aziridines (103) (Scheme IB.34). Hoffman[211] et al have demonstrated that the same ylide (101) can also affect other C-N duoble bond systems when he synthesised 1-azacyclobutanes (105) by the direct condensation of the ylide (101) with aziridines (104) (Scheme IB.35).

However, the stabilized sulfonium ylides differ from the non stabilized sulfonium ylides in so far as their course of reaction with schiff's bases is concerned and it was observed[212] that ylides (106) produce arylaminocinnamates (108) and not aziridines (Scheme IB.36).

2.10.4 With C-S double bonds: Synthesis of Thioxirane

Corey and Chaykovsky[142] have reported that methylene dimethyl

sulfurane (109) on its reaction with benzothiophenone (110) affects the methylene transfer at C=S bond affording the thiooxirane (111). The reaction follows the same course as with bonzophenone (Scheme IB.37).

2.10.5 With N-O double bond

The reaction of nitro compound with sulfonium ylides leads to the synthesis of C-N double bond. Johnson[163] demonstrated that it was fairly on addition, elimination methylene transfer reaction on π-sulfuranes which produces oxime. Thus fluoranylidenedimethyl sulfurane (112) and nitrosobenzene (113) were shown to under go an exothermic and rapid reaction to afford the nitrone-N-phenylfluorenone ketoxime (114) (Scheme IB.38).

IB.2.11 Metalation of π-sulfuranes

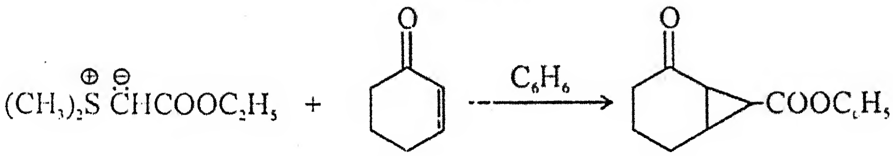
The metalation reaction of π-sulfuranes could not be explored until recently only preliminary studies on the reactions of inorganic compounds with the yields are reported[147].

However it has been shown that the sulfonium ylides (115) being co-ordinatively unsaturated-1,2 dipolar complex of carbon serve as a good ligand for transitional metals (116) in various oxidation states and yields the markedly stable metal complaxes (117) of sulfonium ylides (115) (Scheme IB.39).

IB.2.12 Elimination

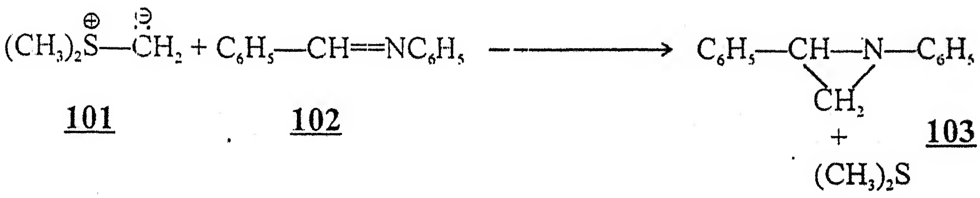
Evidence for the α-elimination is meagre[213]. However, dimethyl

SCHEME IB.33



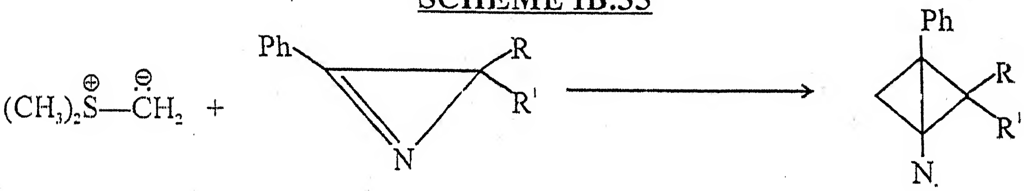
98 99 100

SCHEME IB.34



101 102 103

SCHEME IB.35



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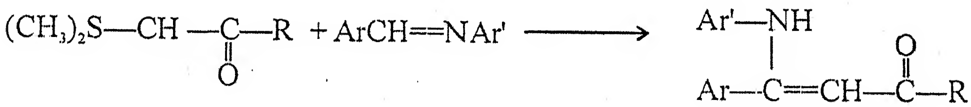
SCHEME IB.36



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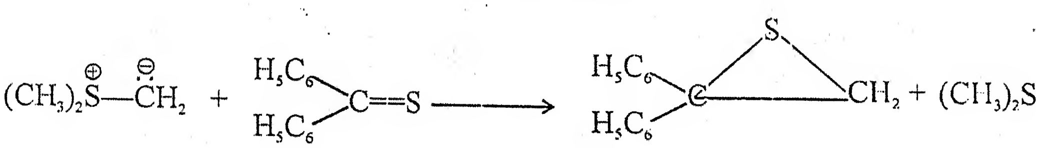
SCHEME IB.37



109 110 111

sulfonium phenacylide (118) has been reported to add on cyclohexene (119) in the presence of cupric sulphate through α-elimination giving cyclopropane (120)[214] other claims of α-elimination remain even more speculative.

IB.2.13 Rearrangement

As revealed by the literature π-sulfuranes have been involved in several types of rearrangements. Thomson and Stevans[215] have reported that benzylmethylphenacylsulfonium bromide (121) undergo of phenacylidene benzylmethyl sulfurane (122) to yield the rearrangement product (123) (Scheme IB.41). Kouser et al[216] have demonstrated that the benzyl dimethyl sulfonium ion (124) in the presence of amide ion undersgoes sommet rearrangement to afford o-methylbenzyl methyl sulfide (125) (Scheme IB.42).

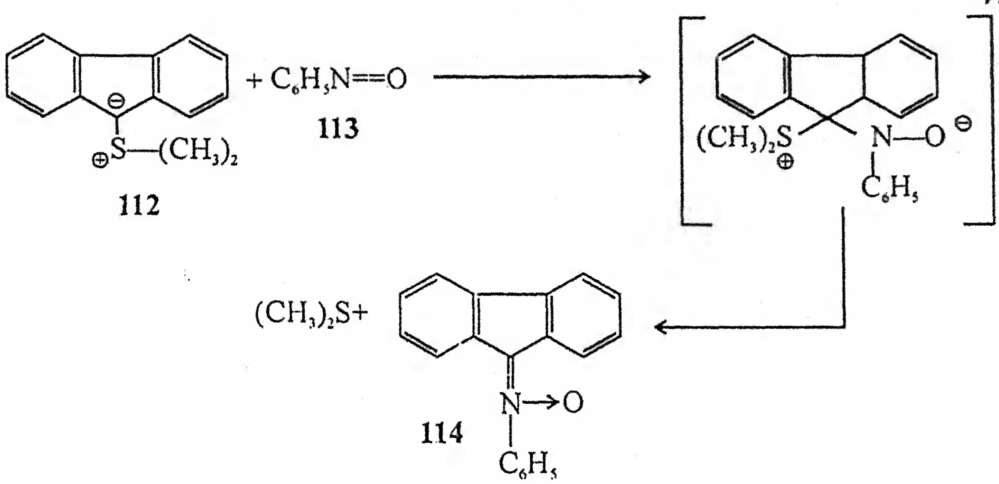
In recent years, these rearrangements have been prdouced to be of great synthetic importance particularily in the synthesis of natural products[181,217].

IB.2.14. π-Sulfurance in the prepration of polymers

In an attempt to prepare sulfonium ylide polymer viz. π-sulfurane polymer Tanimoto and et al[218,219] carried out the reaction of sulfonium salt with benzaldehyde in presence of base and obtained styrene oxide. The reaction was carried out to proceed via ylide polymer formation (126) which was unstable and has not been isolated.

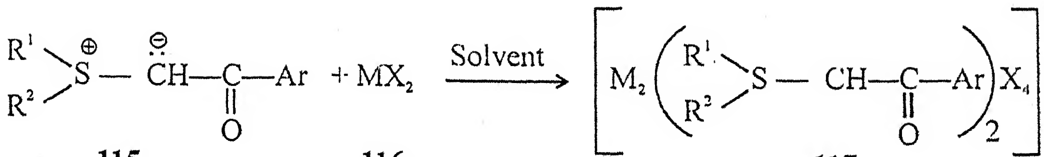
Latter on, Kondo et al[220] reported the synthesis of poly (vinyl

SCHEME IB.38



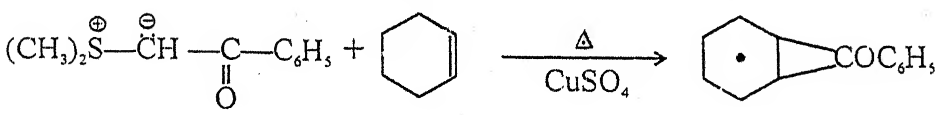
112 113 114

SCHEME IB.39



115 116 117

SCHEME IB.40



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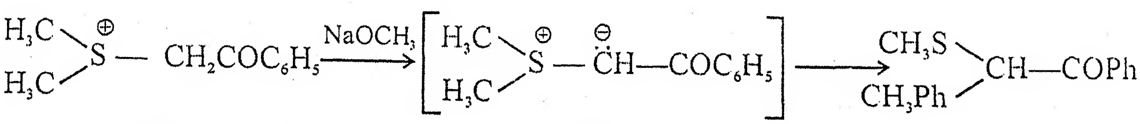
SCHEME IB.41



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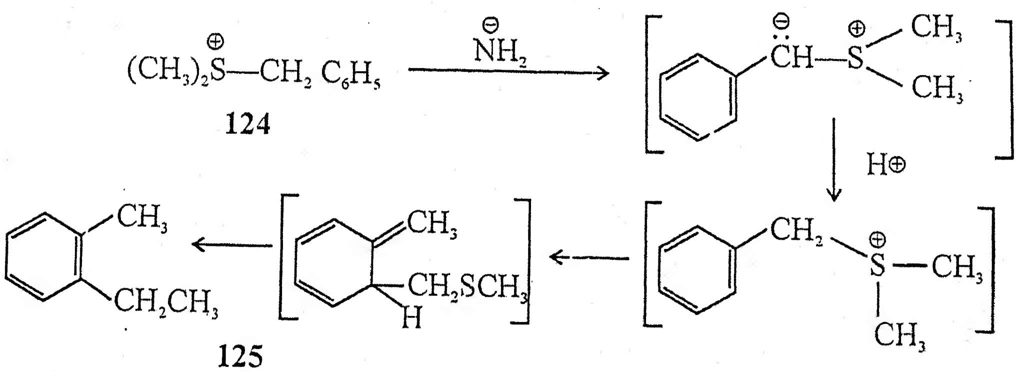
SCHEME IB.42



124 125

sulfonium ylide) with a trivalent sulfur attached directly to the polymer chain, Poly (styryl vinyl sulfonium bis (methoxycarbonyl) methylide (127) was prepared by irradiating of a benzene solution of poly (ethyl vinyl sulfide) and dimethyl diazomalonate in a pyrex tube by a high pressure mercury lamp. In the similar manner, an attempt was made to prepare poly (Phenyl vinyl) sulfonium bis (methoxy carbonyl) methylide] (128), but it was not successful. However, the compound was obtained by the thermal reaction of diazomalonate and poly (phenylvinyl sulfide) in the presence of cupric sulphate as catalyst in benzene.

The structure of these ylide polymers were determined and confirmed by IR and NMR spectra. These were the first stable sulfonium ylide polymers reported in the literature[220]. They are very important for some industirial uses as ion exchange resins, polymer supports, peptide synthesis, polymeric reagents and polyelectrolytes. Also in 1977, Hess Mereau[221] found that when poly (α-vinyl pyridine) was quaternized, these polyelectrolyte products were subjected to thermal decomposition at 7200°C to give isocyanic acid or its isomer, cyanic acid. The addition of base to the solution of electrolyte in water gave a yellow polymeric ylide.

In a pioneering article, farrall et al[222] reported the preparation of fully regenerable sulfonium salts anchored to an insoluble polymer

and their ylides with carbonyl compounds. Their results clearly indicate that phase transfer catalysis is the method of choice for the generation of sulfonium ylides on insoluble resins from a polymeric sulfonium salt.

Kondo maintained his interest in this area and with his collaborators[220] he made detailed investigation on the polymerisation and preparation of methyl-4-vinyl phenyl-sulfonium bis(methoxy carbonyl) methylide (129) as a new kind of stable vinyl monomer containing the sulfonium ylide structure. It was prepared by heating a solution of 4-methyl thiostyrene, dimethyldiazomalonate, and t-butyl catechol in chlorobenzene at 90^{0}C for 10 hours in the presence of anhydride cupric sulphate and (129) was polymerized by useing α-α' axobisisobutyronitrile (AIBN) as initiator and dimethylsulfoxide as solvent at 60^{0}C. The structure of polymer was confirmed by IR and NMR spectra and elemental analysis. In addition, this monomeric ylide was copoly-merised with vinyl monomers such as methyl methacrylate (MMA) and styrene.

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Chapter-II

Chapter -II

REACTION OF SOME NEW SUBSTITUTED PHENACYLIDENEPYRIDINIUM YLIDES WITH α, β-UNSATURATED KETONES : SYNTHESIS OF SOME NEW 2,4,6-TRIARYL PYRIDINES AND 2,4-DAIRYL-6-(β-PHENYLVINYL) PYRIDINES VIA CARBONYL STABILIZED PYRIDINIUM YLIDES*

II.1 Abstract

Interactions between m-substituted phenacylpyridinium ylides and a wide variety of α,β unsaturated ketones have been investigated and shown to involve a potential route for the synthesis of 2,4,6-triarylpyridines. 3-chlorophenacylpyridinium ylide, 3-methylphenacylpyridinium ylide, 3-methoxyphenacylpyridinium ylides, 3-ethoxyphenacylpyridinium ylide when reacted with a variety of α,β-unsaturated carbonyl compounds using ammonium aceteate in glacial acetic acid or methanol as cyclization agent, afforded 2-(3-chlorophenyl)- 4,6-diaryl, 2-(3-methylphenyl) -4, 6-diaryl, 2-(3-methoxyphenyl) -4,6-diaryl, 2-(3-ethoxyphenyl) -4,6-diaryl pyridines respectively. Reactions of these pyridinium ylides with dibenzalacetones in mixture of ammonium acetate & glacial acetic

* A part of work has been communciated in Proc. Nat. Acad. Sc. (Allahabd) India, 1908

acid gave 2, 4-diaryl-6-(β-phenylvinyl) pyridines in 50-70% yields. The compounds gave satisfactory elemental analysis. The product have been characterised on the basis of analytical IR and NMR spectral data.

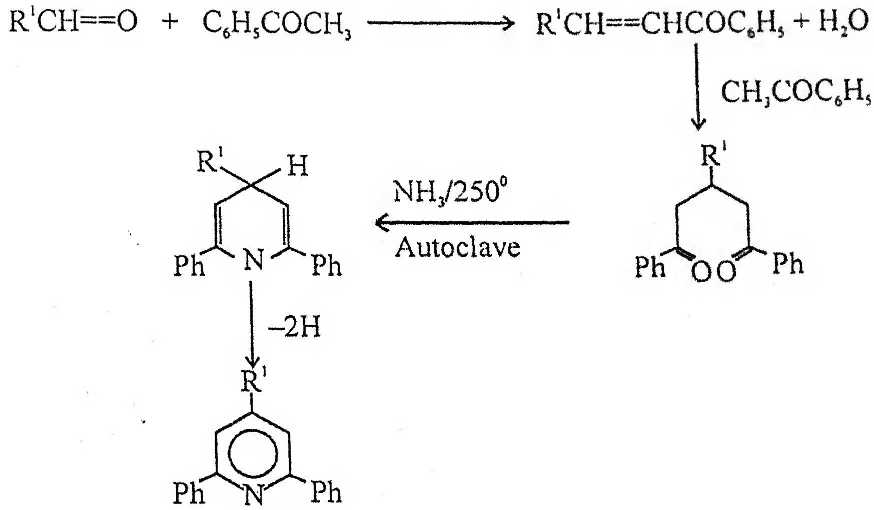
II.2 Introduction

One of the earlier methods, involving aza ring closure leading to the synthesis of substituted pyridines, was reported by Tschitschibabin[1]. The method involves the condensation of aldehyde and methyl ketone in presence of liquid ammonia (Scheme II.1). But this route is not versatile because of it requires harsh reaction conditions and gives poor yields of the pyridines. Subsequent to this report, Frank et al[2,3] made an improvement by using ammonia and catalytic amounts of ammonium acetate.

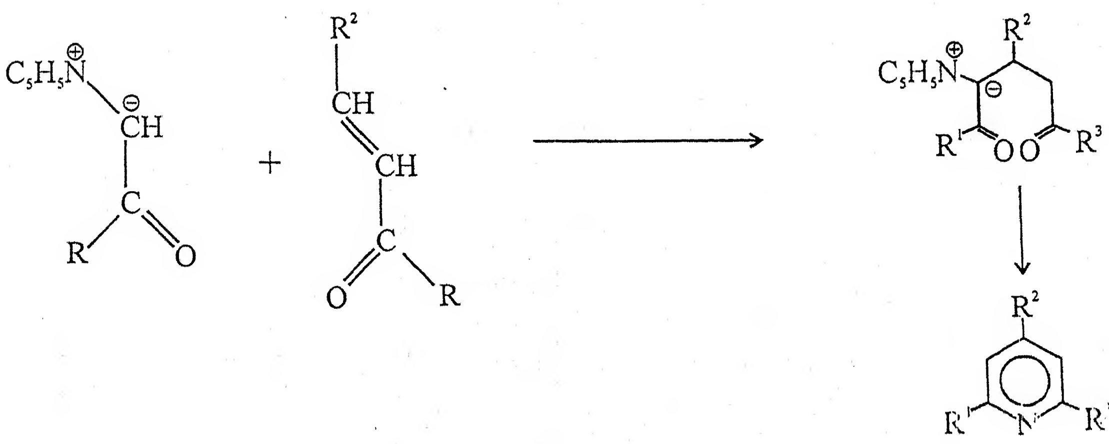
Later Krohnke et.al.[4,5] developed a superior method for synthesis of pyridines. This method involves the interaction of pyridinium salt or ylides with α,β -unsaturated ketones (Scheme II.2). The course of the reaction involves the same pentane-1,5-diaryl intermediate, analogous to the diketone intermediate formed in earlier methods.[1-3] The intermediate undergoes the azaring closure with ammonium acetate in glacial acetic acid to give 2,4,6-triarypyridines. The superiority of Krohnke's method[4,5] over that of Tschitschibabin's method[1] lies in milder conditions and better yield of pyridines.

Moreover, earlier methods[1,3] were restricted to the preparation

SCHEME II.1



SCHEME II.2



of symmetrical pyridines having identical substituents at 2 & 6-positions of the pyridinring. The Krohnke's method[4,5] allows the synthesis of both symmetrical and asymmetrical pyridines having diffrent substituents at 2,4 & 6 positions of pyridine nucleus.

It was, therefore, thought worth while to investigate the domain of synthetic applicability of pyridinium ylides. In the present chapter we have reported the synthesis of some asymmetrical 2,4,6-triaryl substitutedpyridines having various different groups by the condensation of substituted phenacyldienepyridinium ylides with substituted benzylideneacetones and dibenzylideneacetones.

II.3. Results and Discussion

Quaternization of pyridine with 4-chlorophenacylbromide, 3-methylphenacyl bromide, 3-methoxyphenacyl bromide in benzene at reflux temperature afforded 3-chlorophenacylpyridinium bromides (1a), 3-methylphenacylpyridinium bromide (1b) and 3-Methoxyphenacyl-pyridinium bromide (1c) respectively. 3-Ethoxyphenacyl pyridinium bromide (1d) was prepared by refluxing 3-Ethoxyphenacyl bromide with pyridine in THF.

Treatment of the salt (1a-d) with aqueous sodium carbonate affected proton abstraction to give their corresponding ylides (2a-d) which, though isolable, can not be stored due to their senstivity towards atmospheric components and hence, could not be used in subsequent reactions. All these reactions were therefore carried out

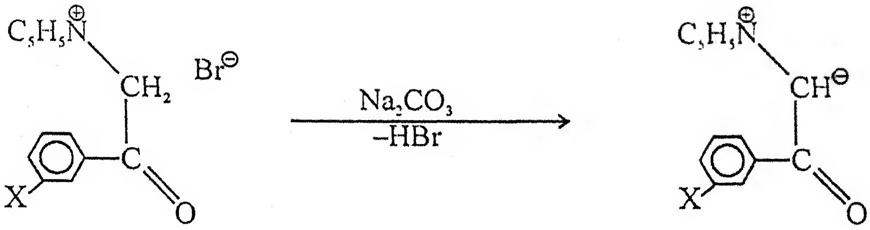
through generation *in situ* of the ylides from their precursors (Scheme II.3).

The structure of salt (1a-d) was evidenced by the comparison of melting point with that reported in literature. The IR spectrum of pyridinium salts (1a-d)[6-8] revealed a characteristic absorption band at 1690 cm^{-1} due to C–O stretching vibrations for the carbonyl group. The diagnostic absorption band in the 3300 cm^{-1} was observed due to C–H stretching vibration of methylene group attached to the nitrogen atom. The NMR spectrum of the salt (1a-d) displayed a peak at δ6.80 (singlet) due to methylene group and other aromatic protons were exhibited in the range δ 7.20-8.45 (multiplet).

Heating a mixture of salts (1a-d) with α,β-unsaturated ketones (3a-o) in the presence of ammonium acetate and glacial acetic acid or methanol at reflux temperature afforded 2-(3-chlorophenyl) -4, 6-diaryl, 2-(3-methylphenyl) -4, 6-diaryl, 2-(4-methoxyphenyl) -4, 6-diaryl, 2-(3-ethoxyphenyl)-4, 6-diaryl pyridines (5a-o) (Scheme II.4). Next the attention was directed towards the synthesis of 2, 4-diaryl -6- (β-phenylvinyl) pyridines (8a-d) which was achieved by refluxing the corresponding salts(1a-b) or ylides (2a-b) with substituted dibenzylideneacetones (6a-d) in presence of ammonium acetate in glacial acetic acid for 6-8hrs in 40-50% yield (Scheme II.5).

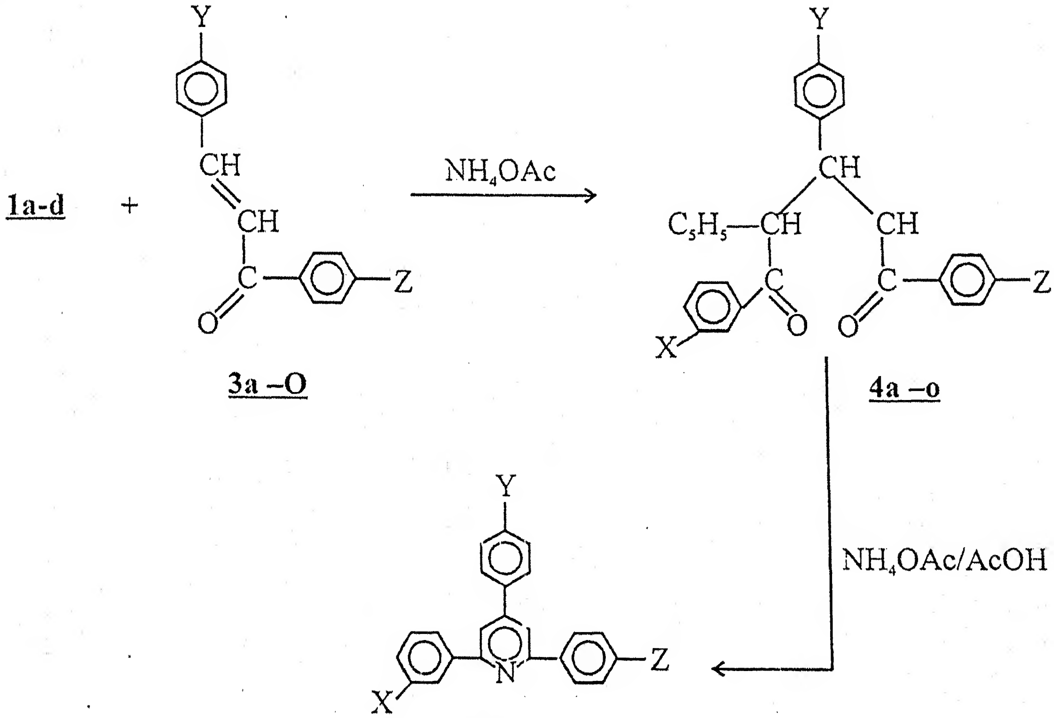
The reaction seems to proceed via pentane 1-5 diaryl

SCHEME II.3



1a-d **2a-d**

SCHEME II.4



3a –O **4a –o** **5a –o**

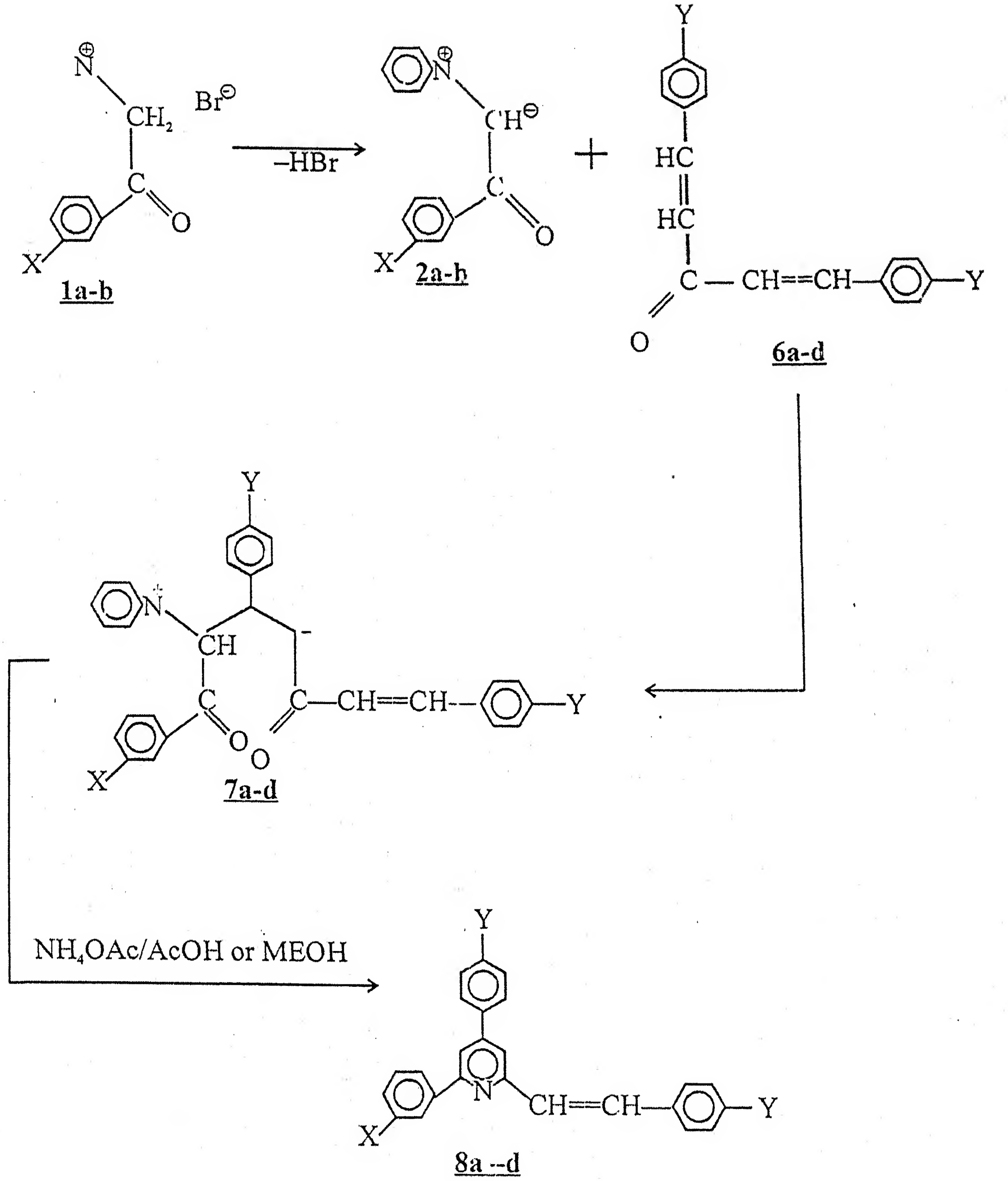
pyridinium derivative (4a-o; 7a-d) formed by the nucleophilic attack of the ylide carbanion on the β-carbon atom of substituted benzylideneacetophenones which then undergo cyclization in presence of ammonium acetate in glacial acetic acid to give 2,4,6-triaryl substituted pyridines (5a-0 & 8a-d).

The substitution on the ylides affects their reactivity and it has been observed that the ylide with electron attracting Cl group is more reactive than the ylide having electron releasing - CH_3, OCH_3 and OC_2H_5 groups. Moreover it has also been observed that 4-ethoxy-phencyl pyridinium ylide is less reactive than 4-methoxy-phenacyl pyridinium ylide. This is possibly due to the steric effect of the bulky -OC_2H_5 group.

The effect of various substitutents on the α,β-unsaturated carbonyl compounds has also been studied and was found that the order of reactivity is dependent on the electronic effect of substituents. Moreover, it has been observed that ortho and para substituted α,β-unsaturated ketones with (–) I effect gave better yields of pyridines than meta analogs. However, it was also observed that reaction was more facile when methanol was used as solvent as compared to that in glacial acetic acid.

All the pyridines (5a-o & 8a-d) gave satisfactory elemental analyses. The structures of products were confirmed by IR and NMR spectral data [9,10]. IR (KBr) spectra in general showed a characteristic

SCHEME II.5



absorption band in the region 3070-3000 cm^{-1}, which are assigned to the C-H stretching mode of pyridine ring. Two bands in the region 1600 cm^{-1} and 1500 cm^{-1} were due to the interactions between C=C and C=N vibration of pyridine ring. The NMR spectra, in general, showed pyridyl protons in the range δ6.90-7.20 and aromatic protons at δ7.00-8.15. The olefinic protons in pyridines (8a-d) were absorbed as quartet in the range δ6.90-7.05).

II.4 Experimental

4.1 General Techniques

Until and unless not specified here and herein after, melting points were recorded in ^{0}C on a Gallen Kamp apparatus and are uncorrected. IR spectra were run on a Perkin-Elmer infracord spectrometer using KBr phase. Varian A-60 and A-100 spectrometers were used to record NMR spectra using tetramethylsilane (TMS) as an internal standard. The products were separated and purified by column chromatography using neutral alumina as adsorbent. Glass microscope slides coated with silica gel G were used for thin layer chromatography (TLC). The spots on slides were developed by placing them in an iodine chamber.

4.2 Starting Materials

All the reagents were obtained from commercial sources (E. Merck, B.D.H., Sisco, Polyforma). Starting materials were prepared according to the procedures reported in literature.[6-8]

4.3 Preparation of m-substitutedphenacylpyridinium bromides (1a-d)

A solution of 100 m mol of m-substitutedphenacyl bromide and 100 mmol of pyridine in 100 ml of anhydroous benzene or tetrahydrofuran was refluxed for 6-8 hrs. The excess of the solvent was evaporated and pet. ether was added to precipitate the salts (1a-d), which were, then, recrystallized from chloroform-pet. ether (1:2) mixture. This procedure was followed to prepare the following salts.

1. 3-chlorophenacylpyridinium bromide (1a) white crystalline solid, m.p. 180-82°C (new).

   IR (KBr) υ_{max} : 1690 (υC=0) 3350 (υ $>\overset{\oplus}{N}$—CH_2), 3010 (υC—H Aryl) :

   NMR ($CDCl_3$) δppm : δ6.70(s, 2H, CH_2); δ7.15–8.25 (m, 9H, ArH)

2. 3-Methylphenacylpyridinium bromide (1b) light reddish crystals.

   m.p. 190°C (new)

   IR (KBr) υ_{max} : 1680 cm^{-1} (υC=0), 3500 (υ $>\overset{\oplus}{N}$—CH_2); 3100 (υC—H Aryl) :

   NMR ($CDCl_3$) δppm :δ6.65 (s, 2H, CH_2); δ2.45(s, 3H, CH_3); δ7.10–8.20 (m, 9H, ArH)

3. 3-Methoxyphenacylpyridium bromide (1c), white crystals, m.p. 200-202^{0}C(new)

IR (KBr) υ_{max}: 1678 cm^{-1} (υC=0); 3575 (υ >$\overset{\oplus}{N}$—CH_2); 3120 (υC—H Aryl) :

NMR ($COCl_3$) δppm: δ6.60 (2,2H,CH_2); δ3.75 (s,3H,OCH_3); δ6.88–8.15 (m, 9H, ArH)

4. 3-Ethoxyphenacylpyridinium bromide, light yellow crystals, m.p. 218-20^{0}C (new).

IR (KBr) υ_{max} : 1688 cm^{-1} (υC=0), 3545 (υ >$\overset{\oplus}{N}$—CH_2); 3725 (υC—H Aryl) :

NMR ($CDCl_3$): δ6.75 (s,2H,-CH_2); δ4.28 (q,2H,OCH_2CH_2): δ1.55 (t,3H,OCH_2CH_3); 7.10-8.30 (m, 9H, ArH).

All the substituted benzylideneacetophenones (3a-o) were prepared by the reaction of substituted benzldehydes and acetopheones in presence of alcoholic sodium hydroxide as reported in literature.

4.4 Preparation of 2,4,6-triaryl pyridines (5a-o)

General procedure

To a stirred mixture of m-substitutedphenacylpyridinium salt (1a-d) (3mmol) anhydrous ammonium acetate (3gm.) in glacial acetic acid (20 ml.), a solution of substituted benzylideneacetophenone (3a-o) (3mmol) dissolved in 20 ml of glacial acetic acid was added

dropwise by a dropping funnel at the reflux temperature in an atmosphere of nitrogen. After complete addition of chalcone, the mixture was refluxed for 5-8 hrs. and then left overnight at room temperature. The mixture was, then poured in ice-cold water (50 ml.) which was constantly stirred. The solid mass was precipitated, filtered and washed twice with water and then with methanol. The product on crystallization with an appropriate solvent gave crystalline titled pyridines (5a-o) in 40-75% yields as shown in table II.1.

4.5 Preparation of 2, 4-diryl -6-(β-phenylvinyl) Pyridines (8a-d)

A mixture of phenacylpyridinium salt (1a-c) (3mmol), ammonium acetate (3g), and glacial acetic acid (50ml) was stirred at 90°C for 2-3 hrs. The substituted dibenzalacetone (6a-b) (3mmol) in glacial acetic acid (20ml) was added dropwise during an hour. The temperature was raised to 120°C and heating was continued for an additional 5-8hrs. The reaction mixture was left overnight at room temperature. Ice water (50ml) was added with constant stirring. The resulting solid mass was filtered, washed twice with water and then methanol, dried and recrystallized from a suitable solvent (Table II.1) to give the pyridines (8a-d).

II.5 REFERENCE

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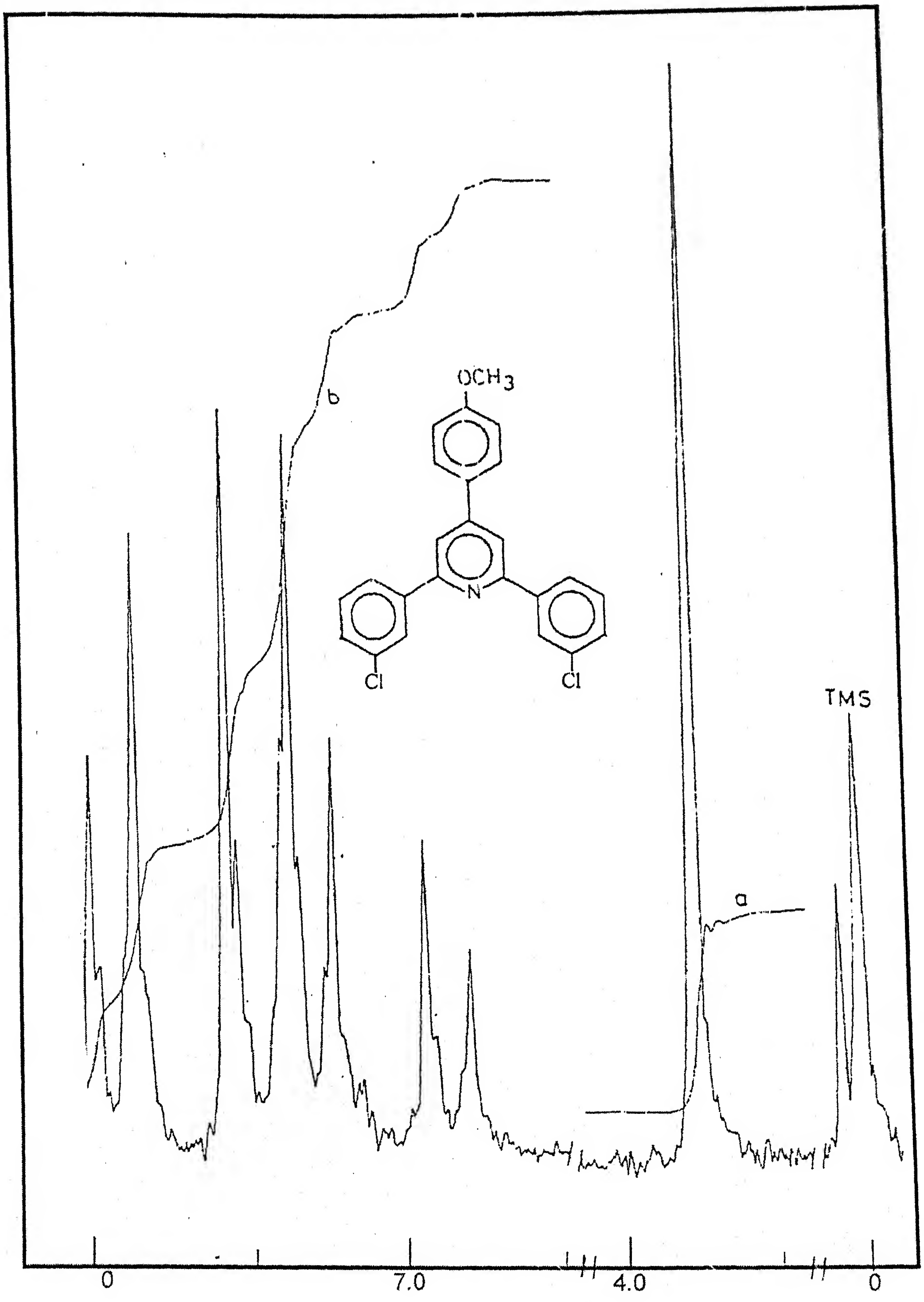

Fig. II 1. NMR spectrum of compound (5e)

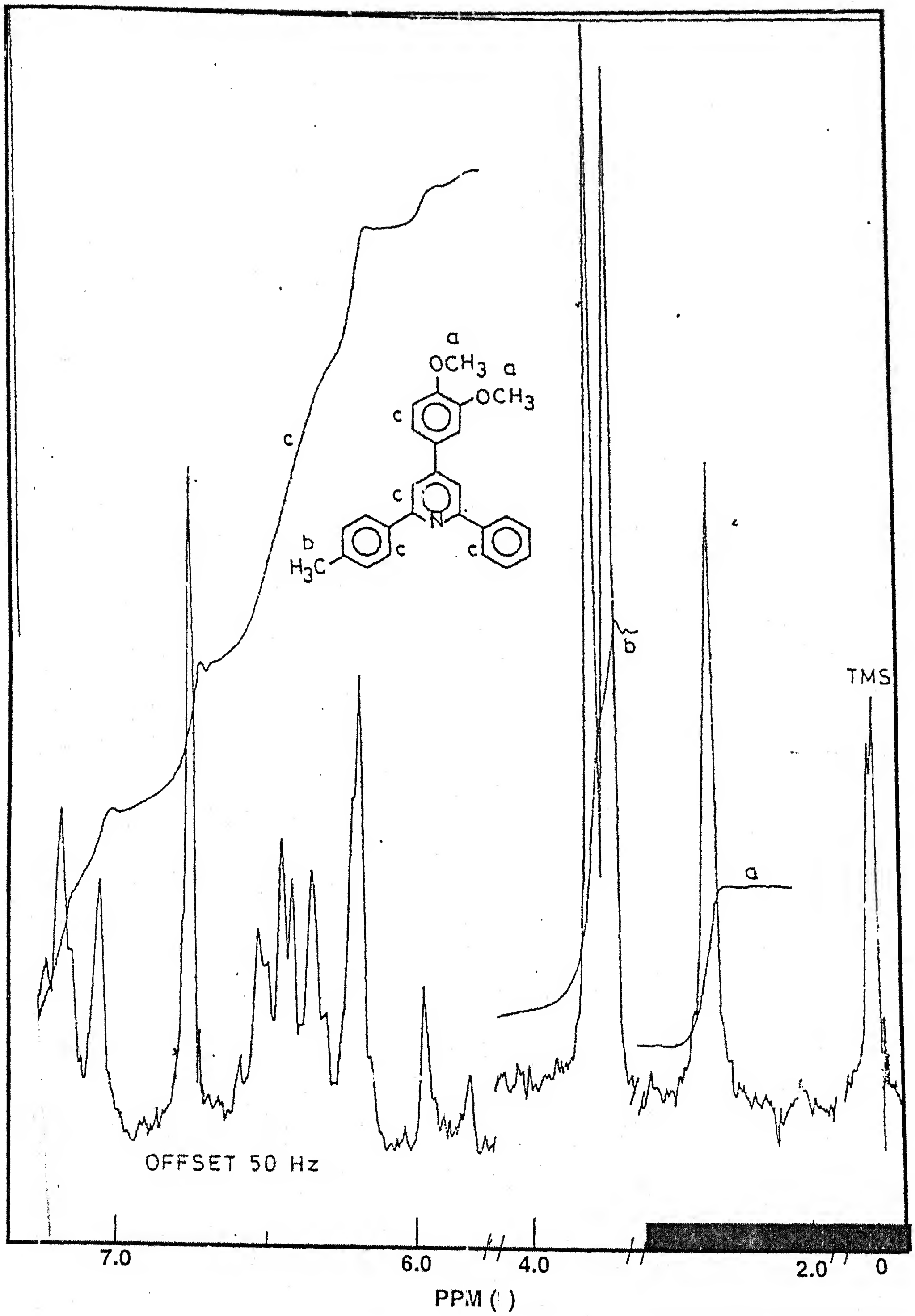

Fig. II 2. NMR spectrum of compound (5g)

TABLE II.1 Physical Properties of 2,4,6-triaryl pyridines (5a-o) and 2,4-diaryl-6- (β-phenyl vinyl) pyridines (8a-d)

Compund	X	Y	Z	Yield %	M.P. °C	Recrystn Solvent	Anal found/(calcd) % C	H	N
1	2	3	4	5	6	7	8	9	10
5a.	3-Cl.C_6H_4	4-Cl.C_6H_4	4-$OCH_3C_6H_4$	40	190-91	Py/MeOH	70.96 (70.93)	4.21 (4.18)	3.47 (3.44)
b.	3-Cl.C_6H_4	4-$OCH_3C_6H_4$	4-$OCH_3C_6H_4$	45	123-25	Py/MeOH	74.68 (74.71)	4.97 (4.98)	3.48 (3.49)
c.	3-Cl.C_6H_4	4-$OCH_3C_3H_4$	4-Cl.C_6H_4	75	176-78	Pyridine	70.98 (70.93)	4.17 (4.18)	3.46 (3.44)
d.	3-Cl.C_6H_4	4-Cl.C_6H_4	4-Cl.C_6H_4	70	above 240	Pyridine	67.25 (67.23)	3.39 (3.41)	3.38 (3.41)
e.	3-$CH_3C_6H_4$	4-$OCH_3C_6H_4$	4-Cl.C_6H_4	45	151-52	Py/MeOH	77.86 (77.82)	5.20 (5.18)	3.65 (3.63)
f.	3-$CH_3C_6H_4$	4-$OCH_3C_6H_4$	4-$OCH_3C_6H_4$	45	116-17	Py/MeOH	82.72 (82.76)	6.12 (6.10)	3.72 (3.71)

Cont Table II.1

1	2	3	4	5	6	7	8	9	10
g.	3-$CH_3C_6H_4$	3,4-$(OCH_3)_2C_6H_3$	C_6H_5	55	97-99	Py/MeOH	82.73 (82.73)	6.08 (6.10)	3.73 (3.71)
h.	3-$CH_3C_6H_4$	4-$N(CH_3)_2C_6H_3$	4-Cl.C_6H_4	62	138-39	Py/MeOH	78.76 (78.79)	5.74 (5.77)	7.00 (7.02)
i	3-$OCH_3C_6H_4$	4-Cl.C_6H_4	4-Cl.C_6H_4	75	195-97	$CHCl_3$/MeOH	70.98 (70.93)	4.15 (4.18)	3.42 (3.44)
j.	3-$OCH_3C_6H_4$	4-$OCH_3C_6H_4$	4-$OCH_3C_6H_4$	55	125-27	$ChCl_3$/MeOH	78.54 (78.58)	5.81 (5.79)	3.54 (3.52)
k.	3-$OCH_3C_6H_4$	4-$N(CH_3)_2C_6H_4$	4-Cl.C_6H_4	60	128-30	$CHCl_3$/MeOH	75.29 (75.27)	5.51 (5.54)	6.70 (6.75)
l.	3-$OCH_3C_6H_4$	4-ClC_6H_4	4-$OCH_3C_6H_4$	75	125-27	Py/MeOH	74.70 (74.71)	5.96 (5.98)	3.45 (3.48)
m.	3-$OC_2H_5C_6H_4$	4-$OCH_3C_3H_5$	3-$NO_2C_6H_4$	60	155-57	$CHCL_3$/n-Hexana	80.71 (80.05)	5.10 (5.19)	4.25 (4.28)

Cont Table II.1

1	2	3	4	5	6	7	8	9	10
n.	3-$OC_2H_5C_6H_4$	4-$OCH_3C_6H_4$	4-Cl.C_6H_4	65	120-22	$CHCl_3$/n-	82.02	5.24	2.15
						Hexana	(82.05)	(5.28)	(2.17)
O.	3-$OC_2H_5C_6H_4$	4-$NO_2C_6H_4$	4-Cl.C_6H_4	60	230-32	$CHCl_3$/n-	78.32	4.24	4.21
						Hexana			
							(78.35)	(4.70)	(4.25)
8a.	3-Cl	H	-	60	140-42	$CHCl_3$/MeoH	81.61	4.85	3.25
							(81.63)	(4.82)	(3.80)
b.	3-Cl	4-OCH_3	-	65	90-92	EtOH/H_2O	75.03	5.24	3.34
							(75.09)	(5.29)	(3.36)
c.	3-CH_3	H	-	65	120-22	$CHCl_3$/MeOH	89.88	6.01	4.02
							(89.91)	(6.05)	4.03)
d.	3-CH_3	4-OCH_3	-	65	142-44	Py/MeOH	82.53	6.13	3.40
							(82.55)	(6.14)	(3.43)

Table II.2 : Spectral data of 2,4,6-triayl pyridines (5a-o) and 2,4-diaryl-6-(β-phenyl vinyl) pyridines (8a-d)

Compound	^{1}HNMR ($CDCl_3$) data			IR (KBr) data Cm^{-1}			
	δ ppm	No. of Protons	Assignment of Protons	C-H	C=C	C=N	C-H
5a	-	-	-	3010	1610	1500	1020
b	-	-	-	3005	1600	1510	1015
c	3.77,s	3H	OCH_3	3040	1605	1510	1010
	6.80-8.20m	14H	aromatic				
d	-	-	-	3010	1605	1500	1010
e	-	-	-	3008	1600	1510	1020
f	-	-	-	3000	1601	1505	1028
g	2.36,s	3H	$-CH_3$	3040	1605	1500	1005
	3.82,d	6H	diOCH_3				
	6.84-8.15,m	14H	Aromatic				
h	2.50,s	3H	$-CH_3$	3030	1615	1510	995
	3.10,s	6H	$-N(CH_3)_2$				
	6.80-8.32,m	14H	Aromatic				
i	3.74,s	3H	$-OCH_3$				
	6.65-8.03,m	14H	Aromatic				
j	3.88,s	9H	$[OCH_3]_3$				
	6.96-8.21,m	14H	Aromatic				
k	-	-	-	3020	1595	1530	1005
l	-	-	-	3030	1600	1540	1020

Cont. Table II.2

Compound	^{1}HNMR ($CDCl_3$) data			IR (KBr) dataCm^{-1}			
	δ ppm	No. of Protons	Assignment of Protons	C-H	C=C	C=N	C-H
m	1.45,t	3H	-OCH_3				
	3.80,s	3H	-OCH_3				
	6.69-8.30,m	14H	Aromaic				
n	-	-	-	2995	1605	1510	990
o	-	-	-	3030	1600	1505	990
8a	7.00,q	2H	-CH=CH-				
	7.12-8.30,	16H	Ar-H +PyH	2998	1610	1500	990
b	7.05.q	2H	-CH=CH-				
	3.85,d J=5.5Hz	6H	dioCH_3				
	7.20-8.15,m	14H	Ar-H+PyH				
c	6.95,s	2H	-CH=CH-				
	2.45,s	3H	-CH_3				
	7.05-8.15,m	16H	Ar-H+PyH				
d	6.90,q	2H	-CH=CH-	3005	1608	1505	990
	2.35,s	3H	-CH3				
	3.90,d, J=6Hz	6H	diOCH_3				
	7.10-8.25,m	14H	ArH+PyH	-	-	-	-

s=singlet d=doublet m=multiplet

Chapter-III

Chapter -III

STUDIES ON THE REACTIONS OF SOME β-PICOLINIUM & γ-PICOLINIUM-YLIDES TOWARDS α,β-UNSATURATED KETONES : SYNTHESIS OF SOME NEW 2,4,6-TRISUBSTITUTEDARYL PRYDINES

III.1 Abstract

A wide variety of symmeterical and unsymmetrical pyridines having different substitutents at 2,4 and 6 positions have been prepared by the ineraction of phenacylidene-β-picolinium-ylide, 4-chlorophenacylidene-γ-picolinium ylide and 4-methylphenacylidene-β-picolinium ylide generated 'in situ' from their precursors, with a wide range of α,β-unsaturated ketones. The ammonium acetate in glacial acetic acid was used as cyclization agent. The structural assignments of the resulting pyridines are based on IR and NMR spectral evidences.

III 2.1 Introduction

One of the earlier reports for the synthesis of arylsubstituted pyridines appears to be stemmed from the work of Tschitschibabin[1] which involves the condensation of aldehyde and ketone in the presence of liquid ammonia (Scheme III.1). But this reaction has received limited attention because of side reactions which affect the yields of resulting pyridines. Following this report, Frank et al.[2,3] in an attempt

to develop reaction conditions which could increase the yields of the products by circumventing the competitive side reactions, have successfully used ammonia and catalytic amount of ammonium acetate. However, this method was proved to be less versatile because of harsh reaction conditions.

Subsequent to these methods, Krohnke et al.[4,5] have reported a superior method which involved the condensation of pyridinium ylide generated ***'in situ'*** with α,β-unsaturated ketones to afford pentane-1,5-dionyl intermediate, analogous to the diketone intermediate formed in the earlier methods,[1-3] the cyclization of which with ammonium acetate in glacial acetic acid gave 2,4,6-trisubstitutedpyridines (Scheme III.2).

This synthesis of substituted pyridines appeared at a first glance to offer improvements over Tschitschibabin reaction[1] as it involved mild reaction conditions and gave products in quantitative yields. Furthermore, Tschitschibabin reaction was restricted to the synthesis of symmetrical pyridines having identical substituents at C-2 and C-6 position of the pyridine nucleus, while Krohnke[4,5] method allowed selective introduction of various phenyl radicals into positions 2,4 and 6. Later on, Tewari & Gupta et al.[6-11] have successfully carried out the synthesis of a variety of 2,4,6-triarylsubstituted pyridines via different pyridinium ylides following Krohnke's synthetic procedure.

An enormous amount of literature[4-11] reveals that exhaustive studies on the reaction of pyridinium ylides towards α,β-unsaturated

ketones have been made during last two decode, and no attention could be paid to study the reaction of methylsubstituted pyridinium ylides i.e., picolinium ylides towards α,β-unsaturated ketones after the only report of Zecher et. al.[5] As the precursors of picolinium ylides, N-acylpicolinium salts were known to have been prepared and their reactions with 1,2-diketones for the synthesis of quinolinium systems (Scheme III.3) have also been reported in the literature.[12] It was, therefore, considered to be of interest to synthesize a variety of β- and γ-picolinium ylides and explore their reactivity towards substituted benzylideneacetophenones in order to shed light on the possible course of the reaction.

III.3 Results and Discussion

Quaternization of β-and γ-picolines with substituted phenacylbromides in benzene at reflux temperature gave substituted phenacyl-β-picolinium and γ-picolinium bromide in almost 70-80% yields[12-15] (Scheme III.4). The structures of the picolinium salts (1a-c) were confirmed by the comparison of melting points of salts with that of reported in literature.[16] The IR spectra (KBr) of the salts (1a-c) showed a characteristic absorption band due to C-O stretching vibration in the region 1700-1600 cm^{-1} for carbonyl group. The diagnostic absorption bands in the region 3300-3000 cm^{-1} were observed due to C-H stretching vibrations of methylene group attached to the nitrogen atom.

Treatment of the salts (1a-c) with aqueous potassium carbonate afforded picolinium ylide, as evident from generation of the coloured precipitates, which were though isolable but could not be stored due to the sensitivity towards atmospheric compoment. The reaction was, therefore, carried out by generating the ylide *'in situ'* from their respective quaternary salts (1a-c) (Scheme III.4).

Heating a mixture of picolinium salts (1a-c) with α,β-unsaturated ketones (2a-u) in the presence of ammonium acetate and glacial acetic acid at reflux temperature le to the formation of 2,4,6-triarylsubstituted -pyridines (4a-u) in 45-65% yields (Scheme III.5). The reaction seems to proceed via intermediacy of the ylide carbanion generated 'in situ' from respective quaternary salts (1a-c) by dehydrohalogenation with acetate ions, which attack on the β-carbon of α,β-unsaturated ketones (2a-u) to afford pentane-1,5-dionyl picolinium derivatives (3a-u), which then undergo aza ring closure with ammonium acetate in acetic acid to give 2,4,6-triarylsubstituted pyridines (4a-u) (Scheme III.5). The 1,5-dionyl intermediate (3a-u) may also be cyclized by means of acetamide and formamide but the ring closure is best carried out in a mixture of ammonium acetate and acetic acid. This mixture promotes the Michael additions of desired type and does not cause acid cleavage of betaine intermediate (3a-u).

Various pyridines (4a-u) synthesized during these studies gave satisfactory elemental analysis. The spectral data of pyridines were

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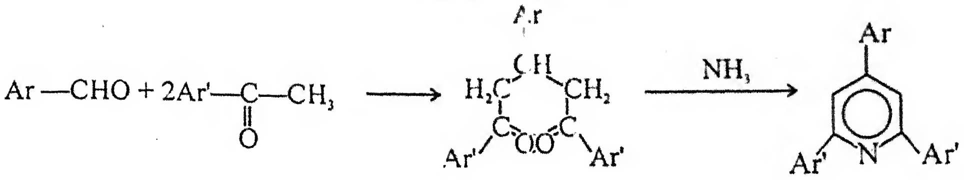

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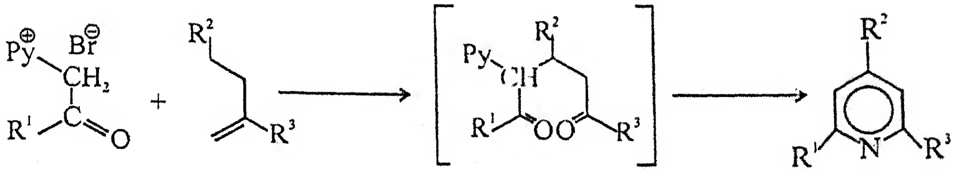

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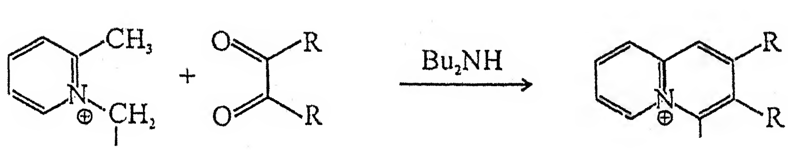

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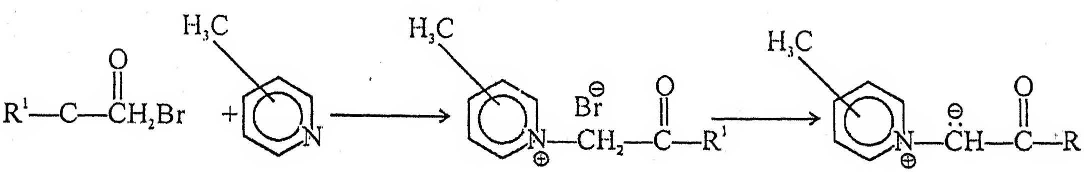
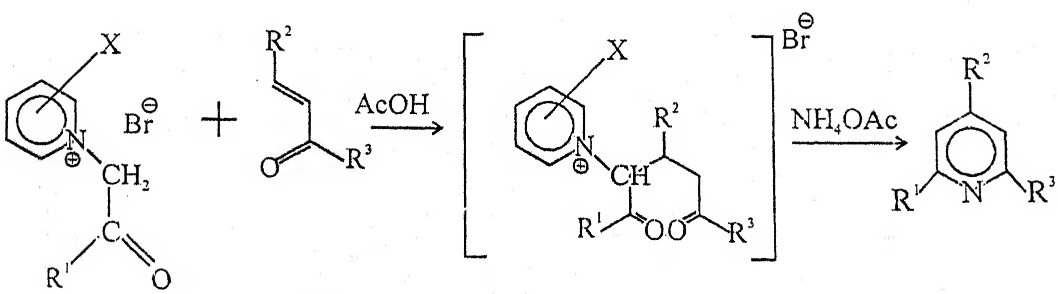


1 a-c

SCHEME III.5



1 a-c   2 a-u   3 a-u   4 a-u

1 a & c, X= 4–CH_3
b, X=3–CH_3

also consistent with the proposed structures. The IR spectra (KBr) of the resulting pyridines in general showed characteristic absorption band in the region 3000 cm^{-1}, which may be assigned to the C-H stretching mode of pyridine rings. Two bands in the region 1600cm^{-1} and near 1500cm^{-1} have been assigned to the interactions between C=C and C=N vibrations of the pyridine rings.[13,14]

III.4 Experimental

4.1 Starting Materials.

All the reagents were obtained from commercial sources (BDH, E. Merck, S. Merck etc.). Starting materials which include ω-bromoacetophenones, were prepared according to the literature cited.[15,16] α,β–unsaturated ketones were synthesized by the method of Gilman and Blatt.[17]

4.2 Preparation of phenacyl-β-picolinium bromide (1a)

To a solution of phenacyl bromide (19.9 g, 0.1 mol) dissolved in 200 ml anhydrous benzene was added dropwise a solution of β-picoline (9.3 g, 100 mmol) with constant stirring at reflux temperature. After 6 h of refluxing, the excess of solvent was evaporated and petroleum ether (60-80^0) was added to it, which caused the precipitation of crude product. The resulting product on recrystallization from rectified spirit gave white shining crystals of phenacyl-β-picolinium bromide (1a), m.p. 215-20^{0}C (lit.[18] 225-30^0 dec.), yield 23.50 g (80%).

Anal. data, found :C, 59.94; H, 4.78; N, 4.76%.

Calcd. for $C_{14}H_{14}$ BrNO : C, 59.90; H, 4.79;N, 4.79%.

IR spectrum (KBr), υ_{max} : 3500 ($>\overset{\oplus}{N}—CH_2$), 3000 (C-H aryl), 1680 cm^{-1} (C=0).

Preparations of 3-chlorophencyl-γ-picolinium bromide (1b)

3-Chlorophenacyl bromide (23.35 g, 0.1 mol) dissovled in 150 ml of anhydrous benzene was set on a steam bath to reflux for 4-6 hrs with an equimolar amount of γ-picoline (9.3 g. 100 mmol). Evaporation of the excess of solvent followed by the addition of petroleum ether (60-80^0), led to the formation of 2-chlorophenacyl-γ-picolinium bromide (1b), which on twice recrystallization from ethanol gave cream coloured crystals of 3-chlorophenacyl-γ-picolinium bromide (7b), m.p. 238-40^{0}C, yield 26g (80%).

Anal. Data, Found : C, 51.56; H, 4.96; N, 4.32%

Calcd. for $C_{14}H_{13}$ BrClNO. : C, 51.53; H, 4.98; N, 4.29%

IR spectrum (KBr), υ_{max} : 3500 ($>\overset{\oplus}{N}—CH_2$), 3010 (C-H aryl); 1690 cm^{-1} (C=0).

Preparation of 3-methylphenacyl-β-picolinium bromide (1c)

The reaction of 3-methylphenacyl bromide (21.3 g, 0.1 mol) and β-picoline (9.3 g, 100 mmol) in 150 ml of anhydrous benzene was heated for 8h under reflux temperature. Excess of solvent was evaporated and petroleum ether (60-80^0) was added to precipitate the crude product which on recrystallization from rectified spirit gave

24.5 g (80%) white needles of 3-methylphenacyl-β-picolinium bromide (1c), m.p. 226-28°C.

Anal. data, found : C, 58.86, H, 5.24; N, 4.62%.

Calcd. for $C_{15}H_{16}$ Br NO : C, 58.82; H, 5.22; N, 4.57%.

Ir spectrum (Kbr), υ_{max} : 3300 ($>\overset{\oplus}{N}—CH_2$) , 3000 (C-H aryl), 1685 cm^{-1} (c=o).

Preparation of 2,4,6-substituted penyl pyridine (4a-u)

General procedure

To a stirred solution of 3-substituted phenacyl-β-picolinium bromide (1a-c) (3 mmol) in 10ml of glacial acetic acid, was added gradually a solution of substituted benzalacetophenone (2a-u) (3mmol) in 20ml glacial acetic acid in the presence of ammonium acetate (3.0 g) under inert atmosphere of nitrogen. The mixture was then refluxed for 4-8 hrs and was kept overnight at room temperature. Then ice-cold water (100 ml) was added to it and the precipitate thus obtained was separated, washed with methanol, dried and crystallized from pyridine-methanol (1:4) to give 50-80% of the titled compounds.

	R^1	R^2	R^3
4a,	C_6H_5	C_6H_5	C_6H_5
4b,	C_6H_5	C_6H_5	4-C_6H_5.C_6H_4
4c,	C_6H_5	4-Cl.C_6H_4	4-Cl.C_6H_4
4d,	C_6H_5	3,4-CH_2O_2.C_6H_3	4-Cl.C_6H_4

4e,	C_6H_5	3,4-$(OCH_3)_2.C_6H_3$	4-$CH_3C_6H_4$
4f,	3-$Cl.C_6H_4$	4-CH_3-C_6H_4	3-$Cl.C_6H_4$
4g,	3-$Cl.C_6H_4$	4-$OCH_3C_6H_4$	3-$Cl.C_6H_4$
4h,	3-$Cl.C_6H_4$	3,4-$CH_2O_2C_6H_3$	3-$Cl.C_6H_4$
4i,	3-$Cl.C_6H_4$	3,4-$(OCH_3)_2.C_6H_3$	3-$CH_3.C_6H_4$
4j	3-$Cl.C_6H_4$	3,4-$(OCH_3)_2.C_6H_3$	C_6H_5
4k,	3-$CH_3.C_6H_4$	C_6H_5	3-$OCH_3.C_6H_4$
4l,	3-$CH_3.C_6H_4$	4-$OCH_3.C_6H_4$	3-$Cl.C_6H_4$
4m,	3-$CH_3.C_6H_4$	4-$OCH_3.C_5H_4$	3-$CH_3.C_6H_4$
4n,	3-$CH_3.C_6H_4$	4-$OCH_3.C_6H_4$	3-$OCH_3.C_6H_4$
4o,	3-$CH_3.C_6H_4$	4-$OCH_3.C_6H_4$	3-$NO_2.C_6H_4$
4p,	3-$CH_3.C_6H_4$	3-$CH_3.C_6H_4$	3-$CH_3.C_6H_4$
4q,	3-$CH_3.C_6H_4$	3,4-$(OCH_3)_2.C_6H_3$	C_6H_5
4r,	3-$CH_3.C_6H_4$	3,4-$(OCH_3)_2.C_6H_3$	3-$CH_3.C_6H_4$
4s,	3-CH_3,C_6H_4	3,4-$(OCH_3)_2.C_6H_3$	3-$NO_2.C_6H_4$
4t,	3-$CH_3.C_6H_4$	4-$N(CH_3)_2.C_6H_4$	3-$Cl.C_6H_4$
4u,	3-$CH_3.C_6H_4$	4-$N(CH_3)_2.C_6H_4$	3-$OCH_3.C_6H_4$

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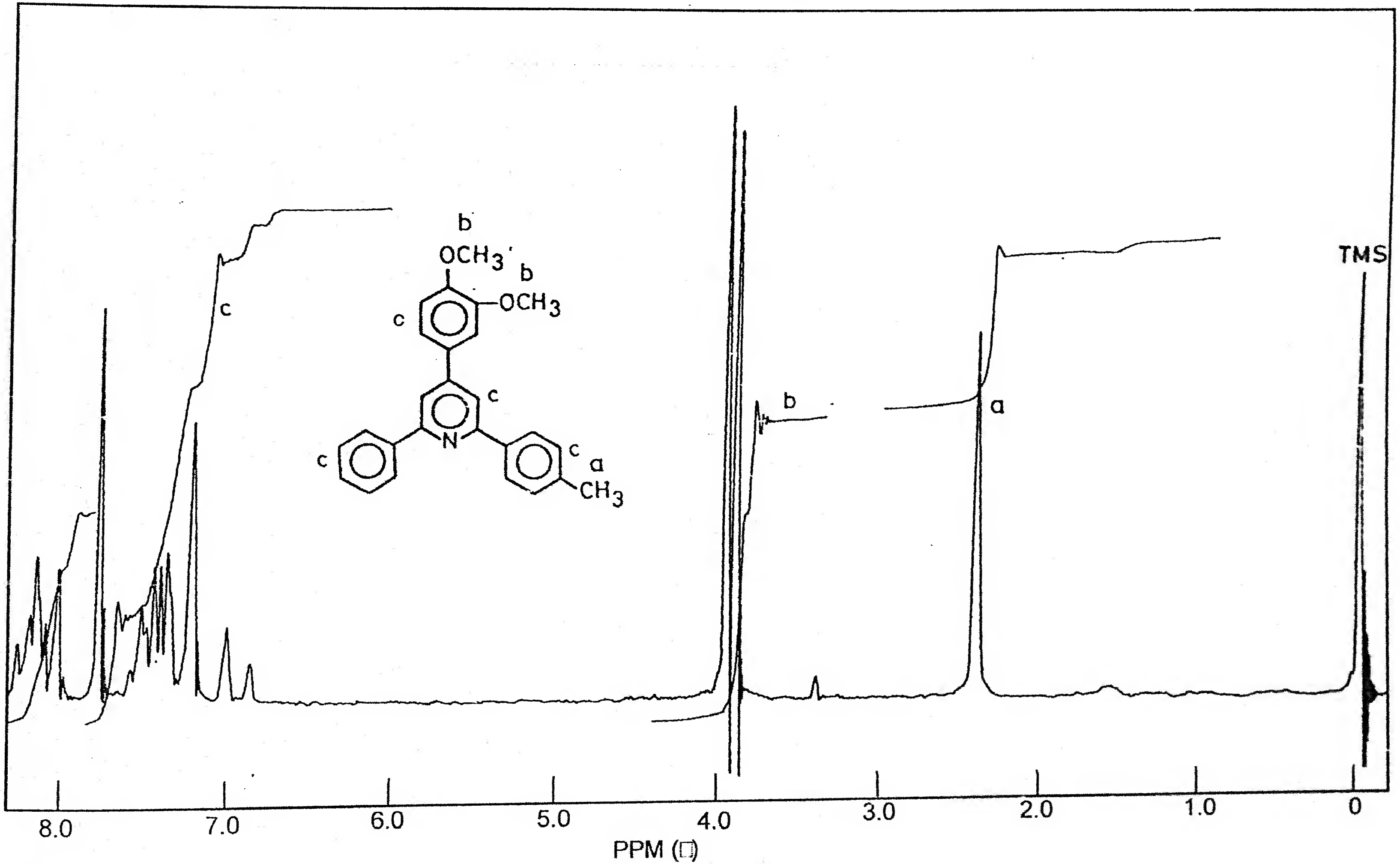

Fig. III 1. NMR spectrum of compound (4e)

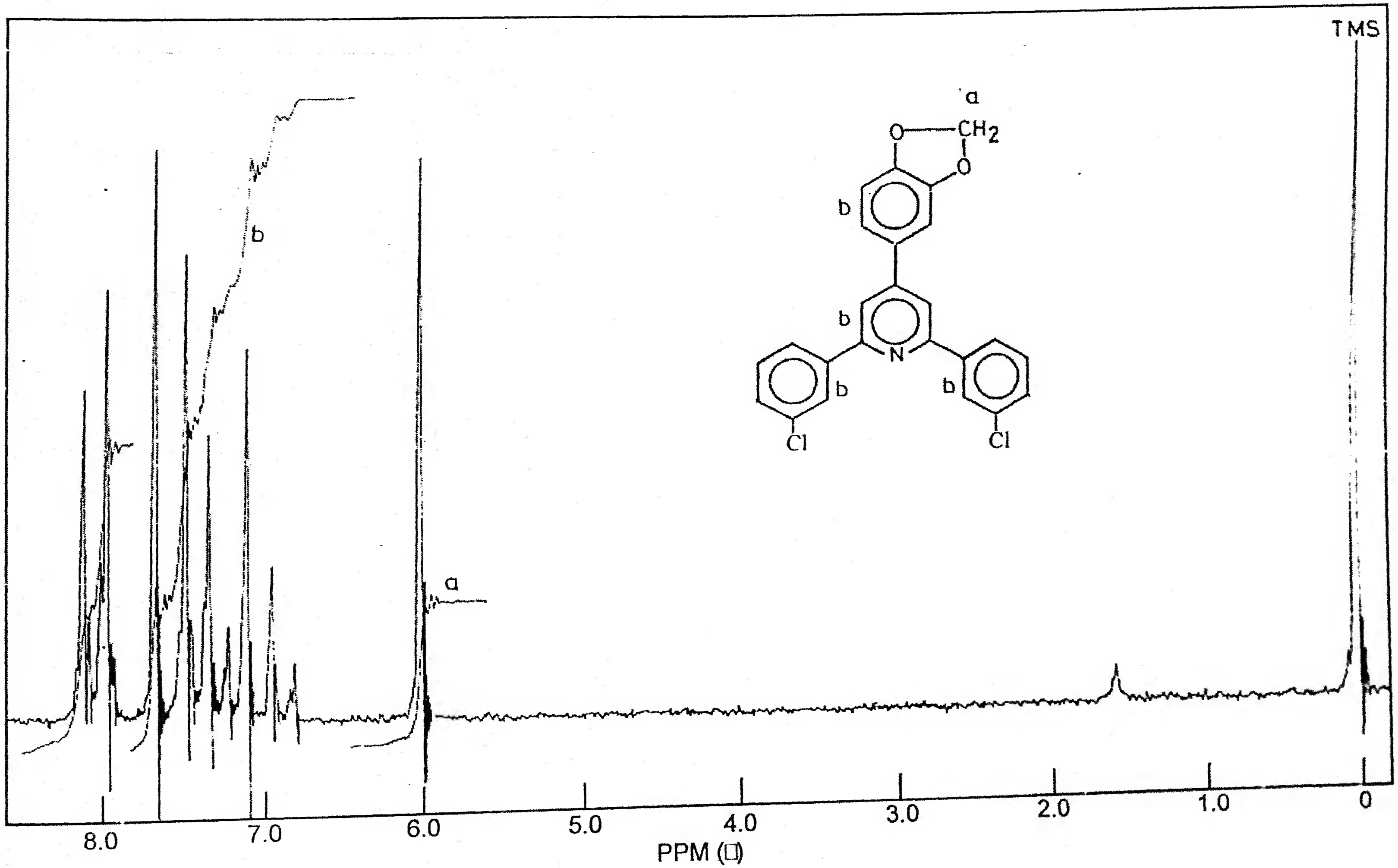

Fig. III.2. NMR Spectrum of compound (4h)

Table III.1 Physical Properties of 2,4,6-triaryl pyridions (11a-u)

Compd.	Yield	m.p °c	Reerystin solvent	Analysis (%):Found (Calcd.) C	H	N
1	2	3	4	5	6	7
4a	60	138-49	A	89.96	5.55	4.60
		(lit[5] 137-39°)		(80.90)	(5.52)	(4.56)
4b	65	130-31	B	90.80	5.5	3.68
				(90.86)	(5.48)	(3.65)
4c	68	134-36	C	73.05	3.98	3.76
				(73.01)	(3.95)	(3.70)
4d	55	152-53	B	84.36	4.95	3.31
				(84.30)	(4.91)	(3.27)
4c	50	112-14	A	81.84	6.01	3.65
				(81.88)	(6.03)	(3.67)
4f	58	170-72	D	81.20	5.41	3.82
				(81.17)	(5.38)	(3.78)
4g	60	178-80	A	70.95	4.21	3.46
				(70.93)	(4.18)	3.44)
4h	65	183-84	B	68.61	3.62	3.38
				(68.57)	(3.57)	(3.33)
4i	60	132-34	A	75.14	5.36	3.32
				(70.09)	(5.29)	(3.36)
4j	50	110-12	C	89.88	5.96	4.21
				(89.82)	(5.98)	(4.19)
4k	45	92-94	A	85.49	5.92	4.04
				(85.46)	(5.98)	(3.98)

Cont. Table III.1

1	2	3	4	5	6	7
4l	55	148-50	B	77.90	5.21	3.68
				(77.82)	(5.18)	(3.63)
4m	50	140-42	C	85.50	6.35	3.88
				(85.47)	(6.30)	(3.83)
4n	45	106-08	B	81.80	6.07	3.74
				(81.88)	(6.03)	(3.67)
4o	55	130-32	A	75.80	5.08	3.58
				(75.75)	(5.05)	(3.53)
4p	62	160-62	D	89.41	6.64	4.05
				(89.39)	(6.59)	(4.01)
4q	45	102-04	A	81.91	6.05	3.72
				(81.88)	(6.03)	(3.67)
4r	65	108-10	C	82.06	6.41	3.61
				(82.02)	(6.32)	(3.54)
4s	60	143-45	B	73.28	5.21	6.61
				(73.23)	(5.16)	(6.57)
4t	50	130-32	A	78.32	5.75	7.06
				(78.29)	(5.77)	(7.02)
4u	55	112-14	D	82.28	6.64	7.14
				(82.23)	(6.59)	(7.10)

A=CH_3OH, B=$CHCl_3$-CH_3OH(1:3) C=C_5H_5M-CH_3OH(1:3)

D=$CHCl_3$-C_6H_6(1:2)

Table III.2 IR and NMR data of 2,4,-6trialpyrimindines (5a-i,6a-i)

Compd.	IR (KBr) (cm^{-1}) data				NMR ($CDCl_3$) data		
	υC-H	υC=C	υ C-N	ϕC-H	(ppm)	No. of protons	Assignments of protons
1	2	3	4	5	6	7	8
4a	3150	1598	1562	1095	-	-	-
4b	3050	1595	1540	1005	-	-	-
4c	3035	1600	1543	1030	-	-	-
4d	3040	1598	1545	1035	6.04,S	2H	OCH_2O
					6.80-8.20,m	19H	ArH
4e	3020	1595	1540	1020	2.35,s	3H	CH3
					3.85-3.90,d	6H	di(OCH3) (J=5Hz)
					6.93-8.13,m	14H	ArH
4f	2950	1600	1550	1005	2.40,s	3H	CH_3
					7.25-8.20,m	14H	ArH
4g	2940	1605	1545	1000	3.75,s	3H	OCH_3
					6.85-8.10	14H	ArH
4h	2980	1600	1520	1018	6.00,s	2H	OCH_2O
					6.90-8.10,m	13H	ArH
4i	2998	1602	15010	1005	2.45,s	3H	CH_3
					3.85-3.90,d	6H	di(OCH_3) (J=5Hz)
					7.05-8.15,m	13H	ArH

Cont. Table III.2

1	2	3	4	5	6	7	8
4j	2950	1600	1510	1005	3.70-3.75,d	6H	di(OCH_3)
							(J=5H_z)
					6.85-7.90,m	14H,	ArH
4k	3005	1595	1515	1015	2.45,2,	3H	CH_3
					6.95-8.40,m	15H,	ArH
4l	3010	1608	1512	1005	2.45,s,	3H	CH_3
					3.78,s	3H	OCH_3
					7.05-8.30,m	14H	ArH
4m	3008	1605	1515	1010	2.55,s	6H	CH_3
					3.90	3H	OCH_3
4n	3015	1000	1500	1015	2.50,s	3H	CH_3
					3.95,s	6H	OCH_3
4o	3010	1610	1515	1025	2.45,s	3H	CH_3
					3.70,s	3H	OCH_3
4p	3020	1600	1525	1020	2.40,s	9H	CH_3
					7.15-8.50,m	14H	ArH
4q	3015	1620	1510	1005	2.35,s	3H	CH_3
					3.78,d	6H	di(OCH_3)
					0.60-8.10,m	14H	ArH

s=singlet d=doublet m=multiplet

Chapter-IV

Chapter -IV

REACTIONS OF SOME AROYLMETHYLENEISOQUINOLINIUM YLIDES WITH α,β-UNSATURATED KETONES: SYNTHESIS OF SOME 2,4,6-TRIARYLSUBSTITUTED PYRIDINES

IV.1 Abstract

The phenacylideneisoquinolinium ylides and 4-phenylphenacylideneisoquinolinium ylides generated *'in situ'* from their respective isoquinolinium salts, react with a wide variety of α,β-unsaturated ketones, particularly substitutedbenzylideneacetophenones to afford 2,4,6-triarylsubstituted pyridines in fair to good yields. The ammonium acetate in glacial acetic acid was used as aza cyclization agent.

The reaction presumbly proceeds via intermediacy of pentane-1,5-dionylisoquinolinium derivative formed by the attack of ylide carbanion on β-carbon atom of α,β-unsaturated ketone.

The structures of the resulting pyridines are based on elemental analytical data which are in good accord with that of calculated values as well as on IR and NMR spectral data.

IV. 2 Introduction~~s~~

Having studied the reactivity of substituted pyridinium ylides so called picolinium ylides in the preceeding chapter, it was thought

logical to divert our attention towards in studying the reactivity of some benzopyridinium ylides which pose the superiority over pyridinium ylide with special reference to the isoquinolinium ylides in as far as the stability of the resulting ylides are concerned. The enhanced stability of these ylides is probably due to the extensive delocalization of the ylidic carbanion over isoquinolinium ring and may be of immense use in characterisation of the ylides.

Although such ylides owe their origin from the earliest investigations made by Krohnke et al.[1] in the year 1935 when they isolated phenacylideneisoquinolinium ylide in the form of enol betaine. But owing to the marked stability and low reactivity, their ability to enter into chemical reactions with a variety of electrophilic reagent remained a point of controversy for considerable length of time. The first report concerning their reactivity appeared in 1935 when Krohnke[2,3] studied the acylation reactions of these ylides. Subsequent to this, Krohnke[4,5] studied the reactions of these ylides with aldehydes which led to the formation of isoquinolinium ethanols (Scheme IV.1). Since then, a flurry of activities started in this area which led to the isolation and characterisation of a wide variety of isoquinolinium-yilides and their reaction products with a wide range of substrates such as C=S,[6] N=O[7,8] nitro[9] etc.

However, no attempts were made to examine the reactivity of these ylides with α,β-unsaturated ketones. The report on this aspect

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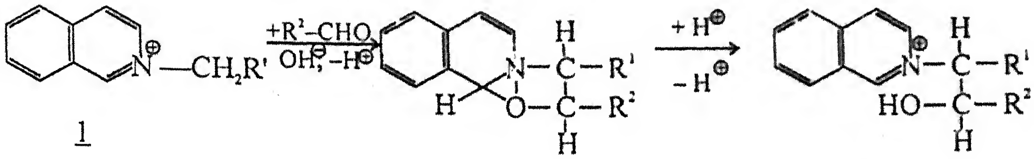
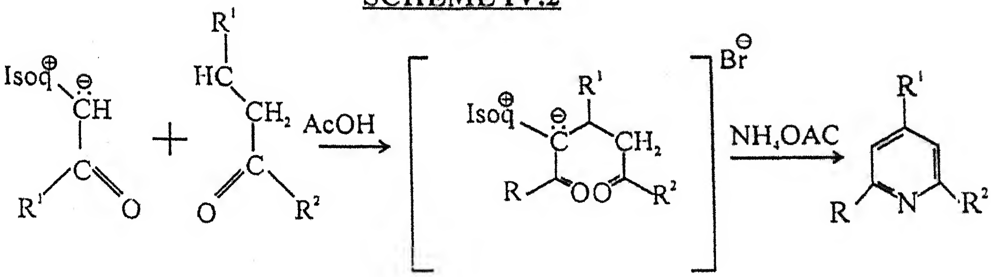


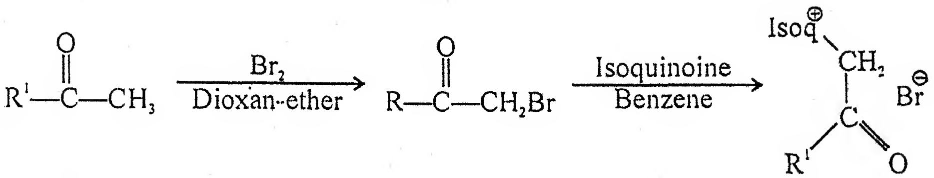
1 2

SCHEME IV.2



3 4 5 6

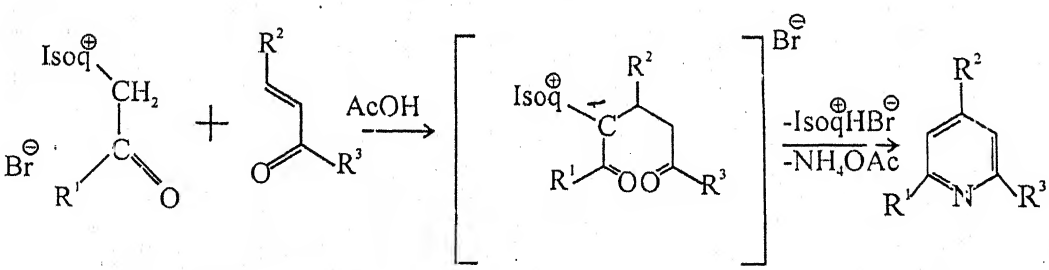
SCHEME IV.3



7 a-b 8 a-b

7, 8 a, R_1=C_6H_5
b, R_1=4-C_6H_5.C_6H_4

SCHEME IV.4



8 a-b 9 a-w 10 a-w 11 a-w

came from Krohnke et al.[10] in the year 1961. When they successfully carried out the reaction of these ylides with α,β-unsaturated ketones and reported the formation of 2,4,6-trisubstituted pyridines (Scheme III.2).

Prompted from this, it was considered to be of interest to examine in the present chapter the reactivity of a wide variety of isoquinilinium-ylides with α,β-unsaturated ketones with a view to project some light on the applicability of these ylides in the synthesis of 2,4,6-trisubstituted pyridines.

IV. 3 Results and Discussion

Bromination of acetophenone and 4-acetobiphenyl in glacial-acetic acid led to the formation of their ω-bromo derivatives, i.e., phenacyl bromide[11] (7a) and 4-phenhylphenacyl bromide[12] (7b) respectively in fair to good yields. Quaternization of these bromides with isoquinoline gave phenacylisoquinolinium bromide (8a) and 4-phenylphenacylisoquinolinium bromide (8b) in almost 80% yield (Scheme IV.3).

The structure of the resulting quaternary-isoquinolinium salts thus synthesized were confirmed on the basis of their literature melting points and spectral evidence as well as elemental analytical data, which are in good accord with that of calculated values. NMR spectra of the salt (8a) displayed a characteristics peak near δ7.0 due to methylene protons adjacent to the nitrogen atom of isoquinoline ring.

Aromatic protons manifested their existence in the range δ7.46-8.41. The IR spectra of the same showed a characteristic band in the region 3300-3000 cm^{-1} due to C-H stretching vibrations. A relatively intense and diagnostic absorption band, owing to the carbonyl stretching vibrations was observed near 1680 cm^{-1}, exhibiting the presence of carbonyl group.

Phenacylisoquinolinium bromide (8a) and 4-phenylphenacyl-isoquinolinium bromide (8b) were allowed to add on a wide range of α,β-unsaturated ketones (9a-w) to form a homogeneous mixture, which on heating at reflux temperature in the presence of ammonium acetate and glacial acetic acid afforded symmetrical and unsymmetrical pyridines (11a-w) (Scheme IV.4). The mechanism of the reaction follows the attack of ylide carbanion, generated 'in situ' by dehydrohalogenation of isoquinolinium salts (8a,b) with acetate ions, on the β-carbon atom of α,β-unsaturated ketones forming an intermediate, pentane-1,5-dionylisoquinolinium derivative (10a-w). The ring closure of these intermediates is brought about in the presence of ammonium acetate to afford 2,4,6-trisubstitutedpyridines. The presence of ammonium acetate promotes Michael addition of the desired type and does not cause the acid cleavage of the intermediate and thus giving the trisubstituted pyridines (11a-w) in appreciable yields (Scheme IV.4).

All the pyridines (11a-w) formed during these studies gave

satisfactory elemental analysis and the structure of the products were supported by IR and NMR spectral evidences.

The infrared spectra of the resulting pyridines (11a-w) manifested a characteristic absorption band in the region 3300-3000 cm^{-1} which may be assigned to the C-H stretching mode of pyridine ring in addition to that of other absorption bands. The two strong absorption bands appeared in the region 1600 cm^{-1} and 1500 cm^{-1} which are diagnostic of the C=C and C=N vibrations of the pyridine ring. The former was in the form of double absorption maxima near 1600 cm^{1} which seems to be a general characteristic of trisubstitution at the pyridine nucleus.[15,14] Two bands in the region 1045 cm^{-1} and 1020 cm^{-1} have been assigned to the ring vibrations and C-H deformations respectively.[13] The nuclear magnetic resonance spectra of the pyridines in general exhibit the aromatic multiplet in the range δ6.80-8.30.

IV.4 Experimental

Starting Material

All the reagents were obtained from commercial source (BDH, E. Merck, S. Merck etc.). Starting material, which include phenacyl bromide,[11] 4-acetobiphenyl,[12] 4-phenylphenacyl bromide[12] were prepared according to the references cited.

α,β-Unsaturated ketones were prepared by the method of Gilmann and Blatt,[15] which involved the stirring of ethanolic solution of aromatic aldehydes with various arylmethyl ketones in equimolar

quantitites in the presence of alkali. This led to the formation of benzylideneacetophenones in 50-90% yields. The crude products were recrystallised from ethanol.

4.1. Preparation of phenylphenacylisoquinolinium bromide (8a)

A solution of isoquinoline (12.9 g, 0.1 mol.) and phenacyl bromide (19.9 g, 0.1 mol) in 100ml of anhydrous benzene was boiled under reflux for 8 h. Excess of solvent was evaporated on a steam bath and petroleum ether (60-80°) was added to precipitate 26.30g (80%) of the phenacylisoquinolinium bromide (8a) The salt was recrystallised twice from ethanol to give light- yellow crystals melting at 205-08°C (lit.[16] 204-06°C).

Anal. data, found	:	C, 62.23, H, 4.30; N, 4.29%.
Calcd. fro $C_{17}H_{14}BrNO$	:	C, 62.19; H, 4.27; N, 4.27%.
IR spectrum (KBr), ν_{max}	:	3300($>\overset{\oplus}{N}-CH_2$) , 3000 (C–H

aryl), 1685cm^{-1} (C=O)

NMR spectrum ($CDCl_3$) [δppm]: 7.07 (s, 2H, $>\overset{\oplus}{N}-CH_2$), 7.46-10.41 (m, 12H, aromatic)

4.2. Preparation of 4-phenylphenacylisoquinolinium bromide (8b)

A mixture containing 27.5 g (0.1 mol) of 4-phenylphenacyl-bromide, 1.29 g (0.1 mol) of isoquinoline and 100 ml of anhydrous benzene was refluxed on a water-bath for 6 h. Excess of solvent was evaporated on a steam-bath and petroleum-ether (60-80°C) was added

to precipitate the crude product which was recrystallised twice from ethanol to give white shining crystals of 4-phenyl-phenacylisoquinolinium bromide (8b), yield, 32.40 g (80%), m.p. 225-26°C (lit.[16] 236°C).

Anal. data, found : C, 68.35; H, 4.48; N, 3.50%

Calcd. for $C_{23}H_{18}BrNO$: C, 68.31; H, 4.45; N, 3.46%

IR spectrum (KBr), ν_{max}: 3315($>\overset{\oplus}{N}-CH_2$) , 3310 (C—H aryl), 1680cm^{-1} (C=O)

4.3 Preparation of 2,4,6-triarylsubstituted pyridines (11a-w)

General procedure

Substitued phenacylisoquinolinium bromide (3 mmol), benzylideneacetophenone (3 mmol), ammonium acetate (3 g) and glacial acetic acid (10 ml) were taken together and subjected to reflux at about 120°C for 4-10 h. After keeping the whole mass overnight at room temperature, 30 ml of ice-cold water was added to it which gave a thick dirty coloured precipitate. This was then washed twice with water and methanol, filtered, dried and crystallised with pyridine-methanol (1:4) to give 2,4,6-triarylsubstituted pyridines (11a-w) in 50-75% yields. The details are given below.

	R^1	R^2	R^3
11a,	C_6H_5	C_6H_5	C_6H_5
11b,	C_6H_5	C_6H_5	$3\text{-}Br.C_6H_4$

11c,	C_6H_5	C_6H_5	3-Cl.C_6H_4
11d,	C_6H_5	C_6H_5	3-$OCH_3C_6H_4$
11e,	C_6H_5	C_6H_5	3-C_6H_5.C_6H_4
11f,	C_6H_5	4-$OCH_3C_6H_4$	3-Cl.C_6H_4
11g,	C_6H_5	4-$OCH_3C_6H_4$	3-OCH_3.C_6H_4
11h,	C_6H_5	4-$OCH_3C_6H_4$	3-$CH_3C_6H_4$
11i,	C_6H_5	4-Cl.C_6H_4	3-Cl.C_6H_4
11j,	C_6H_5	3,4-CH_2O_2.C_6H_3	C_6H_5
11k,	C_6H_5	3,4-CH_2O_2.C_6H_3	3-BrC_6H_4
11l,	C_6H_5	3,4-CH_2O_2.C_6H_3	3-C_6H_5.C_6H_4
11m,	C_6H_5	3,4-$(OCH_3)_2$.C_6H_3	3-$CH_3C_6H_4$
11n,	C_6H_5	C_6H_5	3-NO_2.C_6H_4
11o,	C_6H_5	4-OCH_3.C_6H_4	3_6H_5
11p,	C_6H_5	4-OCH_3.C_6H_4	3-NO_2.C_6H_4
11q,	C_6H_5	2-C_4H_3O	C_6H_5
11r,	4-C_6H_5.C_6H_4	C_6H_5	3-C_6H_5.C_6H_4
11s,	4-C_6H_5.C_6H_4	C_6H_5	3-$OCH_3C_6H_4$
11t,	4-$C_6H_5C_6H_4$	3,4-CH_2O_2.C_6H_3	3-C_6H_5.C_6H_4
11u,	4-$C_6H_5C_6H_4$	C_6H_5	3-$CH_3C_6H_4$
11v,	4-$C_6H_5C_6H_4$	4-$CH_3C_6H_4$	3-$CH_3C_6H_4$
11w,	4-C_6H_5.C_6H_4	3,4-$(OCH_3)_2$.C_6H_3	3-$CH_3C_6H_4$

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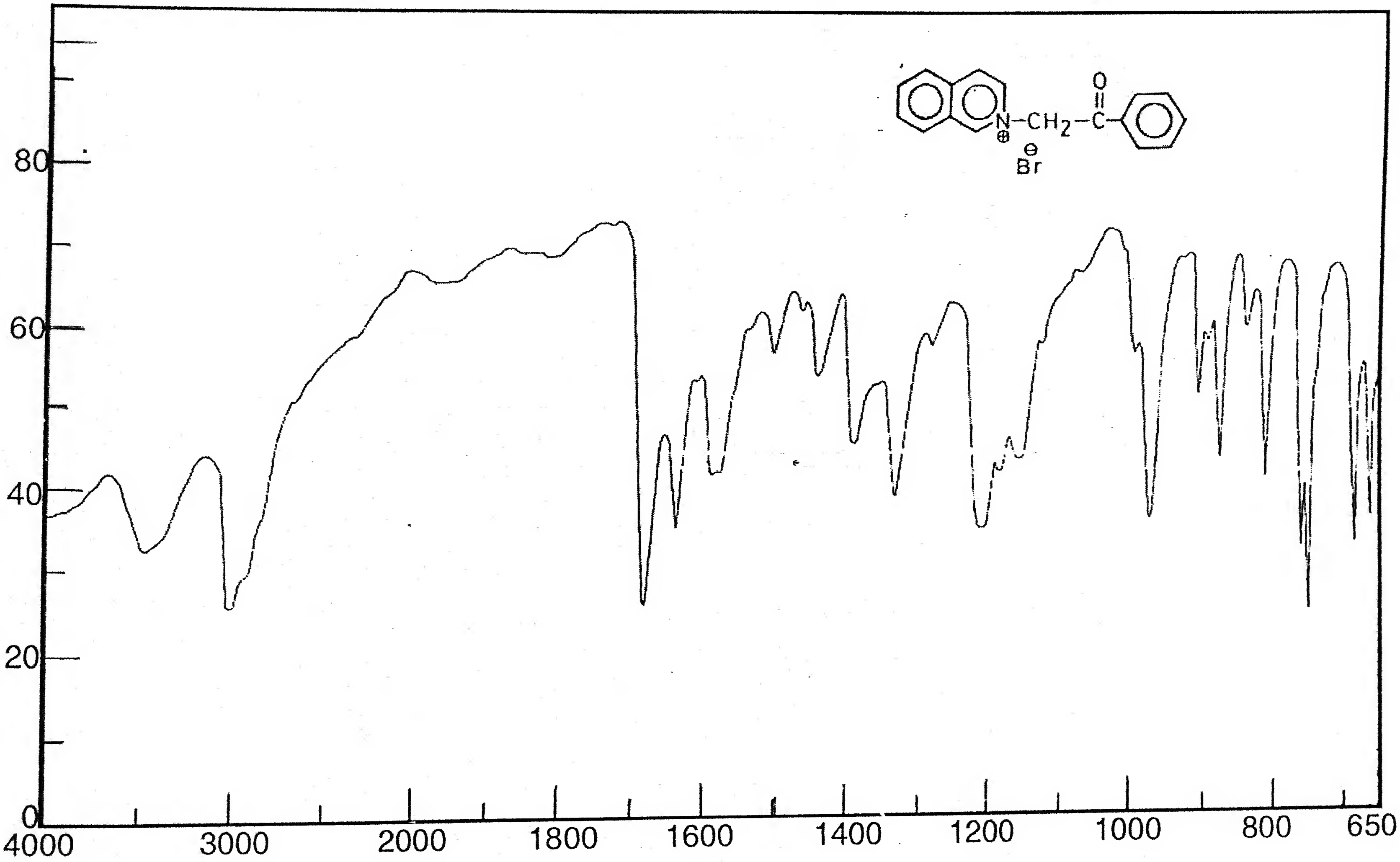


Fig. IV 1. IR spectrum of compound (8a)

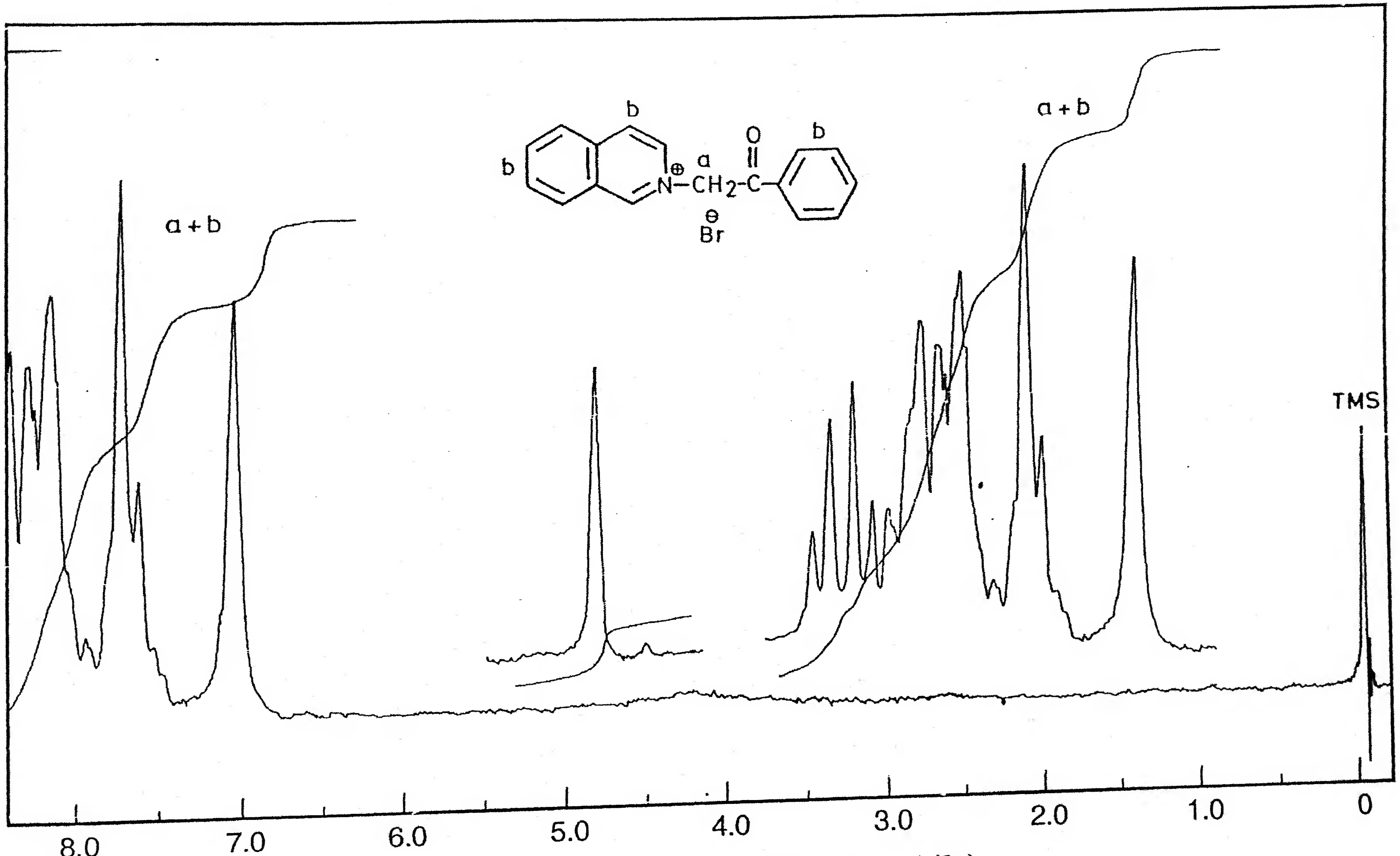


Fig. IV 2. NMR spectrum of compound (8a)

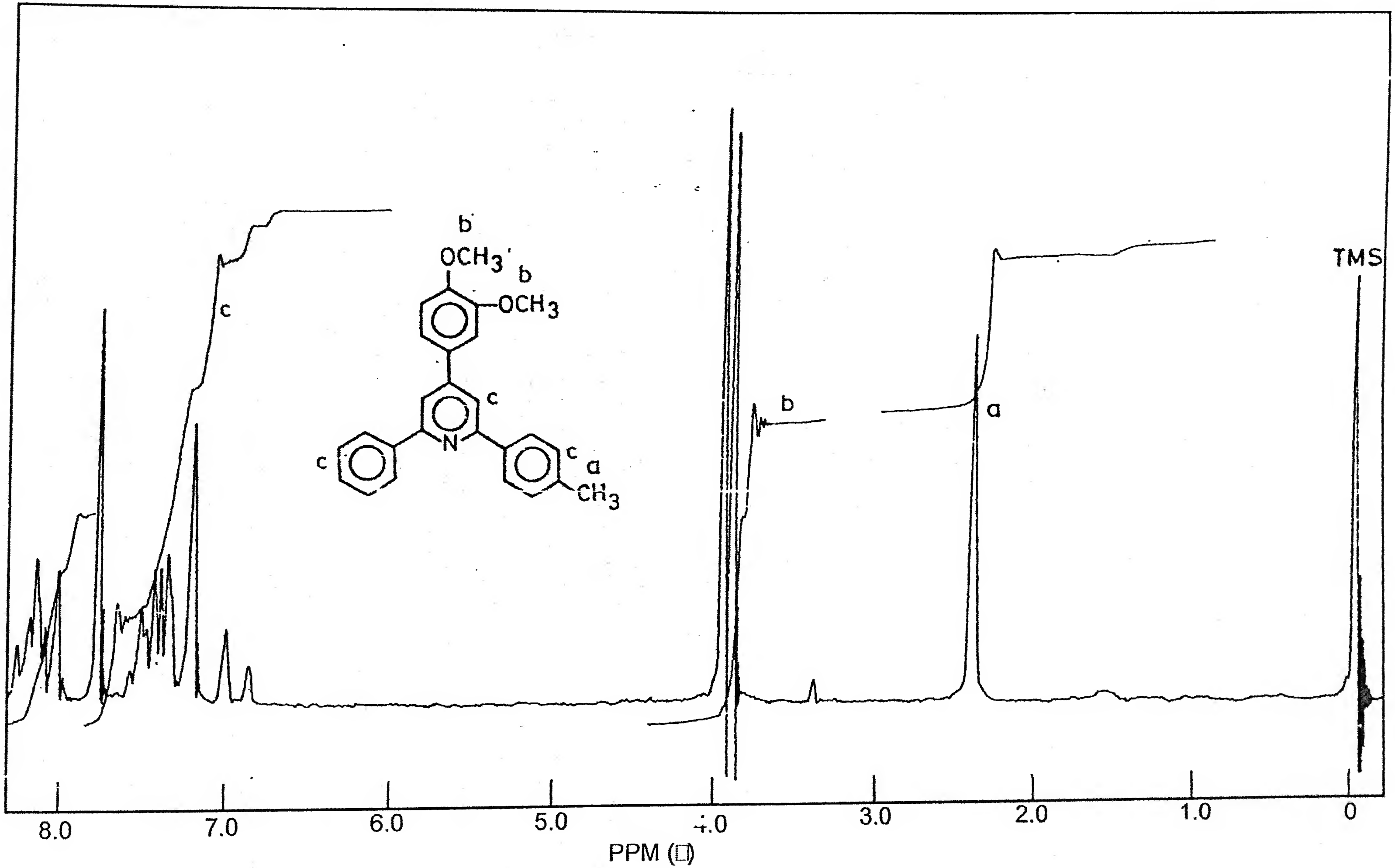


Fig. IV 3. NMR spectrum of compound (11m)

Table IV.1 Physical Properties of 2,4,6-triarylpyridines (11a-w)

Compd.	Yield	m.p ^{0}c	Recrystin solvent	Analysis (%):Found/(Calcd.) C	H	N
1	2	3	4	5	6	7
11a	60	138-39	A	89.93	5.59	4.59
				(89.90)	(5.53)	(4.56)
11b	55	152-53	B	71.53	4.16	3.68
		(lit[17]150-52)		(7.50)	(4.14)	(3.02)
11c	50	125-27	A	80.78	4.66	4.04
				(80.81)	(4.68)	(4.09)
11d	55	105-07	C	84.49	4.90	3.25
				(84.45)	(4.92)	(3.27)
11e	60	138-40	A	90.80	5.42	3.69
				(90.81)	(5.48)	(3.65)
11f	50	110-12	C	77.57	4.89	3.79
				(77.52)	(4.86)	(3.76)
11g	55	102-04	A	81.78	5.78	3.84
				(81.74)	(5.73)	(3.81)
11h	65	122-23	C	85.52	5.92	4.02
				(85.47)	(5.98)	(3.98)
11i	55	138-40	A	73.45	3.94	3.76
				(73.40)	(3.98)	(3.72)
11g	60	152-54	A	82.10	4.80	3.92
		(lit[18].152-53)		(82.05)	(4.84)	(3.98)
11k	50	138-40	C	66.92	3.76	3.28
				(66.97)	(3.72)	(3.25)

Contd. Table IV.1

1	2	3	4	5	6	7
11l	65	154-56	B	84.34	4.94	3.22
				(84.30)	(4.91)	(3.27)
11m	60	120-22	A	81.90	6.08	3.69
				(81.88)	(6.03)	(3.67)
11n	50	127-29	C	78.45	4.51	7.98
				(78.40)	(4.57)	(7.95)
11o	55	90-92	A	84.88	5.66	4.21
				(84.86)	(5.63)	(4.15)
11n	60	101-03	B	78.36	4.94	3.85
				(78.30)	(4.89)	(3.80)
11q	55	158-60	C	84.56	5.11	4.73
				(84.52)	(5.05)	(4.71)
11r	65	192-93	A	91.47	5.47	3.02
				(91.54)	(5.44)	(3.05)
11s	55	135-37	C	87.12	5.54	3.34
				(87.16)	(5.56)	(3.38)
11t	45	240-42	B	85.80	4.90	2.74
				(85.88)	(4.97)	(2.78)
11u	55	172-74	A	90.70	5.84	3.56
				(90.68)	(5.79)	(3.52)
11v	50	176-78	C	90.56	5.12	3.38
				(90.51)	(5.08)	(3.40)
11w	60	78-80	A	84.06	5.94	3.09
				(84.02)	(5.90)	(3.06)

A=C_5H_5N–CH_3OH (1:3), B=$CHCl_3$:CH_3OH(1:3) C=Cl+Cl_3:C_6H_6(1:2)

Table IV.2 IR and NMR data of 2,4,6-trialpyridines (4a–u)

Compd.	IR (KBr) (cm^{-1}) data				NMR ($CDCl_3$) data		
	υC-H	υC=C	υ C-N	ϕC-H	(ppm)	No. of protons	Assignment of protons
1	2	3	4	5	6	7	8
11a	3150	1598	1505	1050	-	-	-
11b	3120	1605	1515	1040	-	-	-
11c	3105	1600	1495	1020	-	-	-
11d	3108	1605	1519	1005	3.75,s	3H	OCH_3
					7.10-8.30,m	16H	ArH
11e	3005	1598	1530	1000	-	-	-
11f.	3025	1605	1508	995	3.90,s	3H	OCH_3
					7.15-8.10,m	15H	ArH
11g	3015	1600	1510	1005	3.75-385,d	6H	di OCH_3 (J=10Hz)
11h	3040	1015	1508	1018	2.50,s	3H	CH_3
					3.95,s	3H	OCH_3
					7.05-8.20	15H	ArH
11i	3155	1610	1515	1010	-	-	-
11j	3130	1620	1530	1030	5.94,s	2H	OCH_2O
					7.15-8.25,m	15H	ArH
11k	3050	1605	1520	1005	5.98,s	2H	OCH_2O
11l	3020	1595	1540	1035	6.05,s	2H	OCH_2O
					6.85-8.20,m	19H	ArH

Contd. Table IV.1

1	2	3	4	5	6	7	8
11m	3010	1505	1545	1020	2.40,s	3H	CH_3
					3.85,s	3H	OCH_3
					3.85-370,d	6H	di (OCH_3) (J=5Hz)
					6.93-8.15,n	14H	ArH
11o	3070	1605	1528	1018	3.90,s	3H	OCH_3
					7.10-8.25,m	16H	ArH
11p	2980	1600	1505	1020	3.95,s	3H	OCH_3
					7.15-830,m	15H	ArH
11q	3050	1605	1540	1030	-	-	-
11r	3000	1590	1550	1080	-	-	-
11s	3020	1600	1510	1030	3.85,s	3H	OCH_3
					6.95-8.15,m	20H	ArH
11t	3045	1615	1525	1020	6.05,s	2H	OCH_2O
11u	3018	1608	1530	1005	2.45,s	3H	CH_3
					7.15-8.30,m	20H	ArH
11v	3055	1620	1535	1005	2.41,s	6H	diCH_3
					7.20-8.30,m	19H	ArH
11w	3045	1610	1530	1010	2.45,s,	3H	CH_3
					3.85-3.90,d	6H	di(OCH_3) (J=5.6Hz)
					7.00-8.40,m	18H	ArH

s=singlet, m=multiplet d=doublet

Chapter-V

Chapter -V

REACTION OF NON STABLE PYRIDINIUM YLIDE WITH α,β-UNSATURATED KETONES : SYNTHESIS OF SOME NEW 1,3-DIARYL-5-NITRO NAPHTHALENES

V.1 Abstract

O-Nitrobenzylpyridinium bromide is prepared by quaternisation of pyridine with o-nitrobenzyl bromide in benzene at reflux temperature. The reaction of salt with α,β-unsaturated ketones in presence of sodium acetate and anhydrous $ZnCl_2$ or $AlCl_3$ at reflux temperature gave 1,3,-diaryl-5-nitronaphthalene in 45-75% yield. Anhydrous $AlCl_3$ oor $ZnCl_2$ in acetic acid is used as cyclization agent. The reaction occurs via intermediacy of betaine formed by nucleophilic attack of ylidic carbanion on β-carbon of α,β-unsaturated ketone. The products were characterized by IR and NMR spectral data.

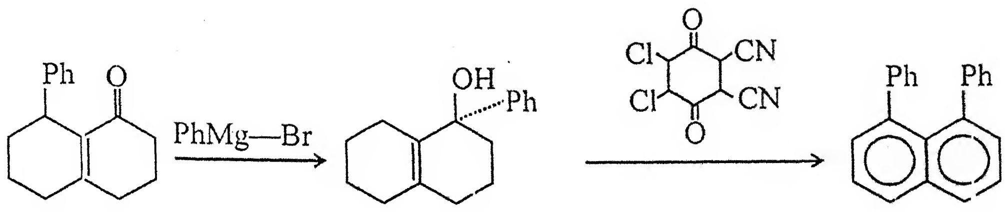
V.2 Introduction

Literature survey reveals that various methods for the synthesis of naphthalene derivatives involve several steps which affect the yield of the final products. The first attempt in this direction was made by House et al[1,2]. who synthesized 1, 8-diphenylnaphthalene (3) by the reaction of 8-phenyloctal-1-one(1) with phenylmagnesium bromide to form an alcohol (2), which underwent dehydrohalogenation and

dehydration with 2,3-dichloro-5,6-dicyanobenzoquinone in boiling benzene to afford the desired product (3) (Scheme V.1). Since this route involved several steps to form the final products. The yield was also poor.

In the subsequent years an alternative route for the synthesis of substituted naphthalenes has been developed[3]. Thus starting from 1,4,5,8,9,10-hexahydro-1,4-dioxo-5-phenylnaphthalene (4) several steps involving reduction, thioketal formation(6) with ethanolic thiol desulfurisation with raney nickel and the subsequent treatment of the resulting product with phenyllithium to give-1-(trans)-hydroxy-(cis) syn-1,8-diphenyldecaline (8) were carried out. The compound (8) on dehydrogenation with Pd/c(30%) yielded 1,8-diphenylnaphthalene (9) (Scheme V.2). Later on, Krohnke et al[4] and Tewari et al[5] have utilized pyridinium salts for the synthesis of trisubstituted naphthalenes (12) and is convenient and facile route which involves the condensation of benzylpyridinium bromide (10) and benzal acetophenone (11) in presence of $ZnCl_2$ or $AlCl_3$ (Scheme V.3). The superiority of this route over earlier methods is that it involves single step and affords good yields of products. Further this route allows the selective introduction of substituents at 1,3,5 positions. However, only a few reactions, following this route, have been reported and detailed experimental condition have not been explored. This prompted us to explore the domain of applicability

SCHEME V.1



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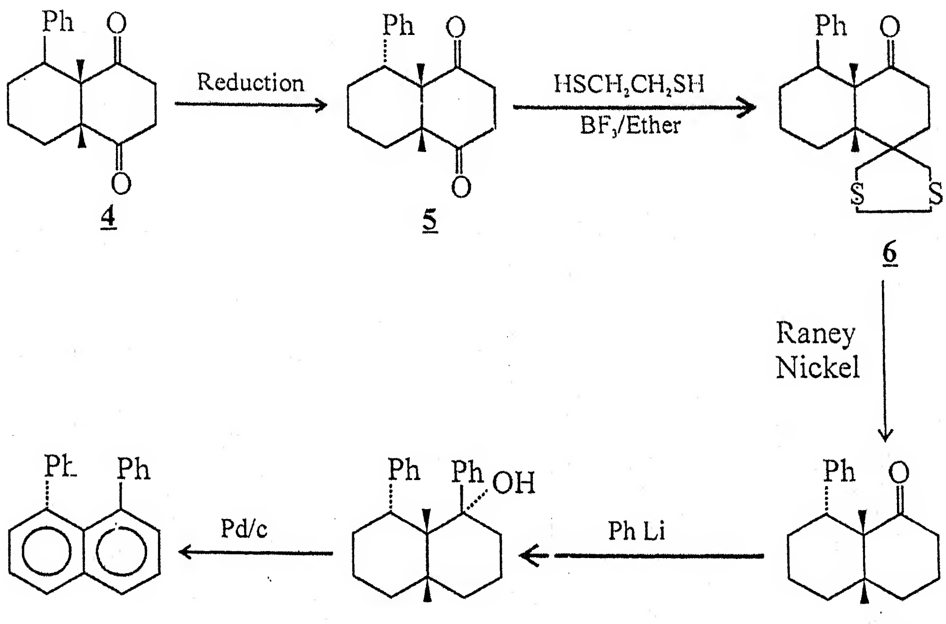
SCHEME V.2



4 5 6 9 8 7

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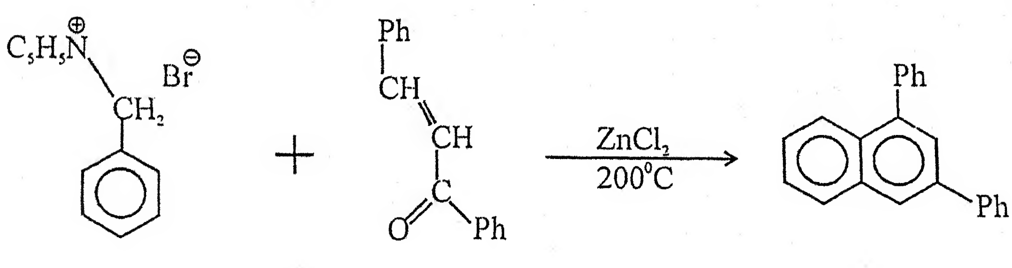


10 11 12

of this route.

In the present Chapter, we have reported the reactions of o-nitrobenzylpyridinium bromide with a wide variety of α,β-unsaturated ketones (Chalcones) in presence of sodium acetate in acetic acid using anhydrous $AlCl_3$ or $ZnCl_2$ as cyclization agent.

V.3. Results and Discussion

The quaternisation of pyridine with o-nitrobenzyl bromide in benzene at reflux temperature gave o-nitrobenzylpyridinium bromide (13) in 80% yield. The structure of salt (13) was evidenced by elemental analysis and spectral data. The IR spectrum of salt (13) showed a diagnostic absorption band of strong intensity at 3045cm^{-1} due to C-H stretching vibration of methylene group attached to a position adjacent to nitrogen atom. The characteristic absorption bands due to NO_2 group in salt (13) were obtained at 1518 cm^{-1} and 1300 cm^{-1}. The NMR spectrum of salt (13) showed a singlet at δ6.35 due to the methylene protons and aromatic protons appeared in the range δ6.80-8.30.

The reactions of these salts (13) were carried out with a wide variety of α,β-unsaturated carbonyl compounds (15a-m) in presence of anhydrous $AlCl_3$ or $ZnCl_2$ in a mixture of sodium acetate and acetic acid at reflux temperature to give 1,3-diaryl-5-nitronaphthalenes (17a-m) in 45-75% yields. It was observed that the yields of resulting products were dependent upon the nature of substituents

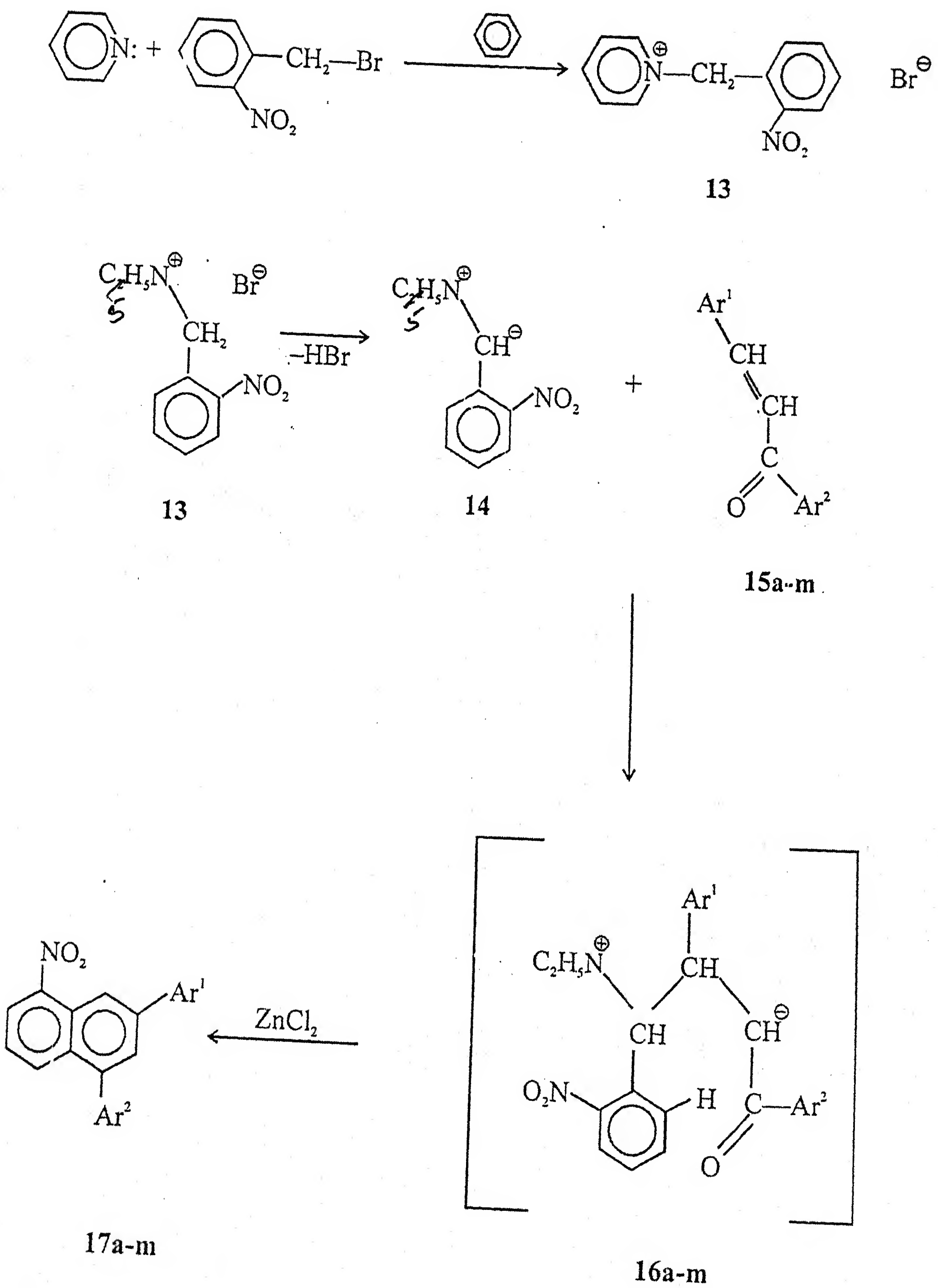
attached to chalcone moities (15a-m) as well as the electron attracting nature of $-NO_2$ group. The salt (13) is more reactive than benzylpyridinium bromide itselt as former gave better yields of products.

The course of reaction seems to be proceeded via the intermediacy of a betaine type of derivative (16), formed by nucleophilic attack of the ylide carbanion (14) on the β-carban of α,β unsaturated ketone. Betaine (16) then undergoes cyclisation in presence of anhydrous $ZnCl_2$ or $AlCl_3$ which is used as cyclization agents to afford naphthalene derivatives (17a-m) (scheme V.4).

All naphthalenes (17a-m) prepared in the present investigations were crystalline solids usually soluble in chloroform, pyridines and acetone. All physical and spectral data have been reported in table V 1-2. All the compounds are new and gave satisfactory elemental analysis. The IR spectral data[6] of pyridines (17a-m) showed a double absorption maxima in the region 1620-1600 cm^{-1} which were assigned to the strethcing vibration of carbon-corban double bond. The strong bands in the region 900-865 cm^{-1} were characteristic absorption of polynuclear aromatics. The nitro group of the naphthalenes showed a diagnostic strong asymmetrical stretching band at 1350-1330cm^{-1}.

The NMR spectral data of the compounds in general showed aromatic multiplet in the range δ6.40-8.50. The methyl and methoxy groups were absorbed in the range δ2.4-2.55 and δ3.70-3.85

<u>SCHEME V.4</u>


N: +
CH2—Br
NO2
N—CH2—
Br
NO2
13
C2H5N
Br
CH2
–HBr
NO2
13
C2H5N
CH
NO2
14
+
Ar1
CH
CH
C
O
Ar2
15a-m
Ar1
C2H5N
CH
CH
CH
O2N
H
C—Ar2
O
16a-m
NO2
Ar1
ZnCl2
Ar2
17a-m

respectively as shown in table V.2.

III. 4. Experimental

Starting Materials

All the reagents were obtained from commercial sources i.e. BDH, S. Merck, E. Merck and SISCO etc. The starting materials were prepared according to references cited. Thus, o-nitrobenzyl-bromide was prepared by direct bromination of o-nitrotoluene at reflux temperature. The substituted benzylidene acetophenones and benzylideneacetonaphthalenes were prepared by stirring the equimolar amount of aromatic aldehyde and acetophenone in ethanolic solution containing NaOH (2%) at 0°C. The resulting precipitate of α,β-unsaturated ketones was recrystallized from ethanol[10].

4.1 Preparation of 0-nitrobenzylpyridinium bromide (13)

A mixture containing 21.5 gm. (100 m mol) of 2-Nitrobenzyl bromide and 7.8g(100 m mol) of anhydrous pyridine in 100ml of anhydrous benzene was refluxed on a water bath for 6-10hrs. The excess of the solvent was evaporated and pet. ether (60-80°C) was added to precipitate 2-nitrobenzylphyridinium bromide (13). This salt was twice recrystallized from chloroform-ethyl acetate (1:2) to give a white crystalline compound.

m.p. 80-90°C. Anal data found : C, 48.50; H, 3.70%

Calcd. for $C_{12}H_{11}BrN_2O_2$: C, 48.81; H, 3.72%

IR spectrum (KBr) $\upsilon_{max.}$ (cm^{-1}); 3040 ($>\overset{\oplus}{N}-CH_2$), 1518 and 1300$cm^{-1}$

(υ–NO_2)

NMR spectrum ($CDCl_3$) (δppm): 6.35 (s,2H,CH_2); 6.80-8.40 (m,9H,Ar-H).

4.2 Preparation of 1,3-diaryl-5-nitronaphthalenes (17a-m)

General procedure

In a 100 ml. R.B. Flask equipped with a reflux condenser and a magnetic stirres, was placed a solution of 2-nitrobenzypyridinium bromide (13) (0.88 g; 3m mol) in 20ml of glacial acetic acid follcwd by the addition of a mixture sodium acetate (1gm) and 2g of anhydrous $ZnCl_2$ or $AlCl_3$. The mixture was stirred at 200°c for 5-10 hrs under a inert atmosphere of nitrogen. The resulting solution was allowed to stand overnight at room temperature. Then ice cold water (25ml) was added. The precipitate solid so obtained was filtered off, deried and chromatographed over neutral alumina. The elution with benzene. & pet-ether gave a fine crystalline solid due to formation of 1,3-diaryl-5-nitronaphthalenes (17a-m) as shown in table V.1.

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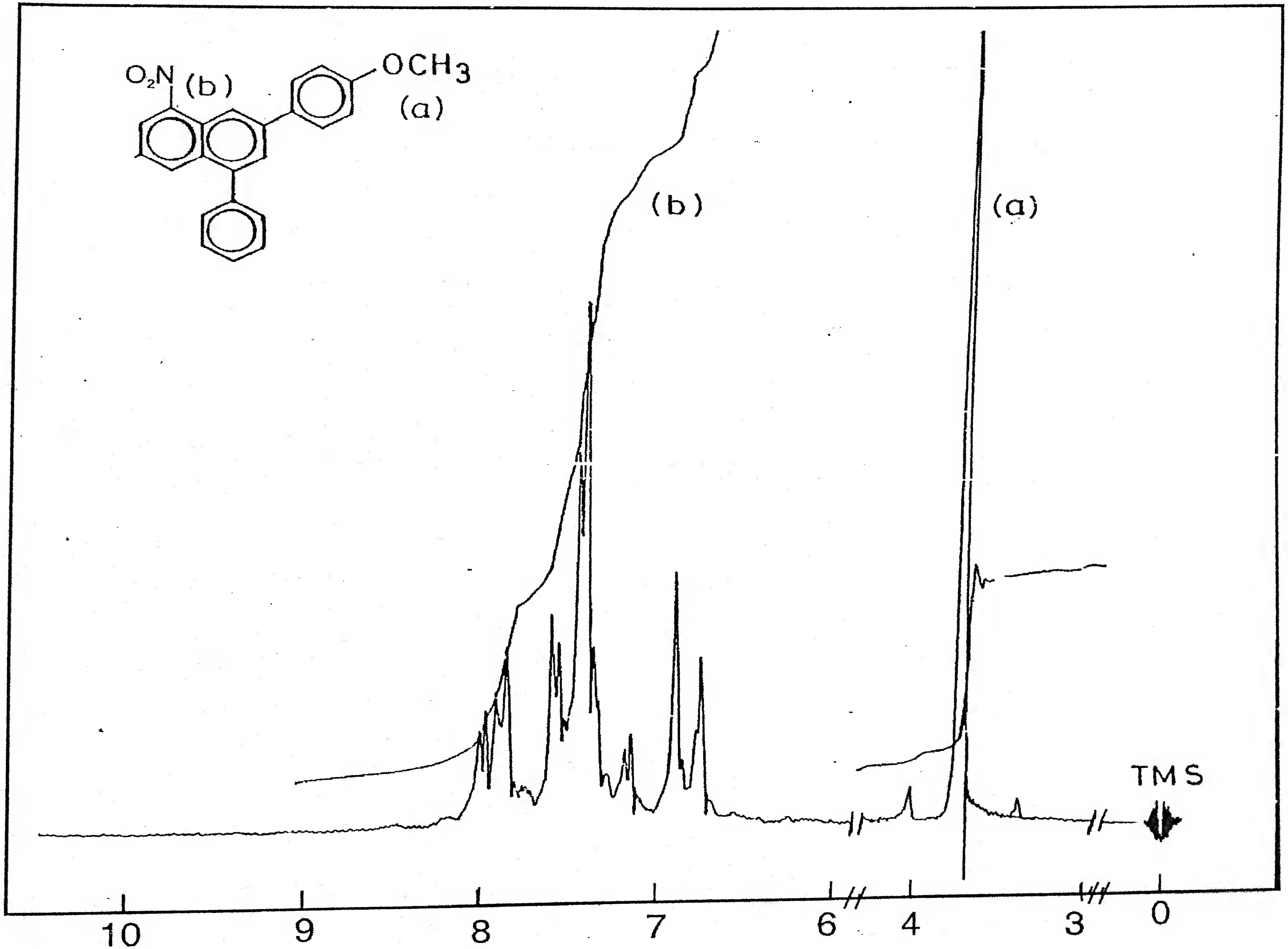

Fig. V 1. NMR spectrum of compound (17c)

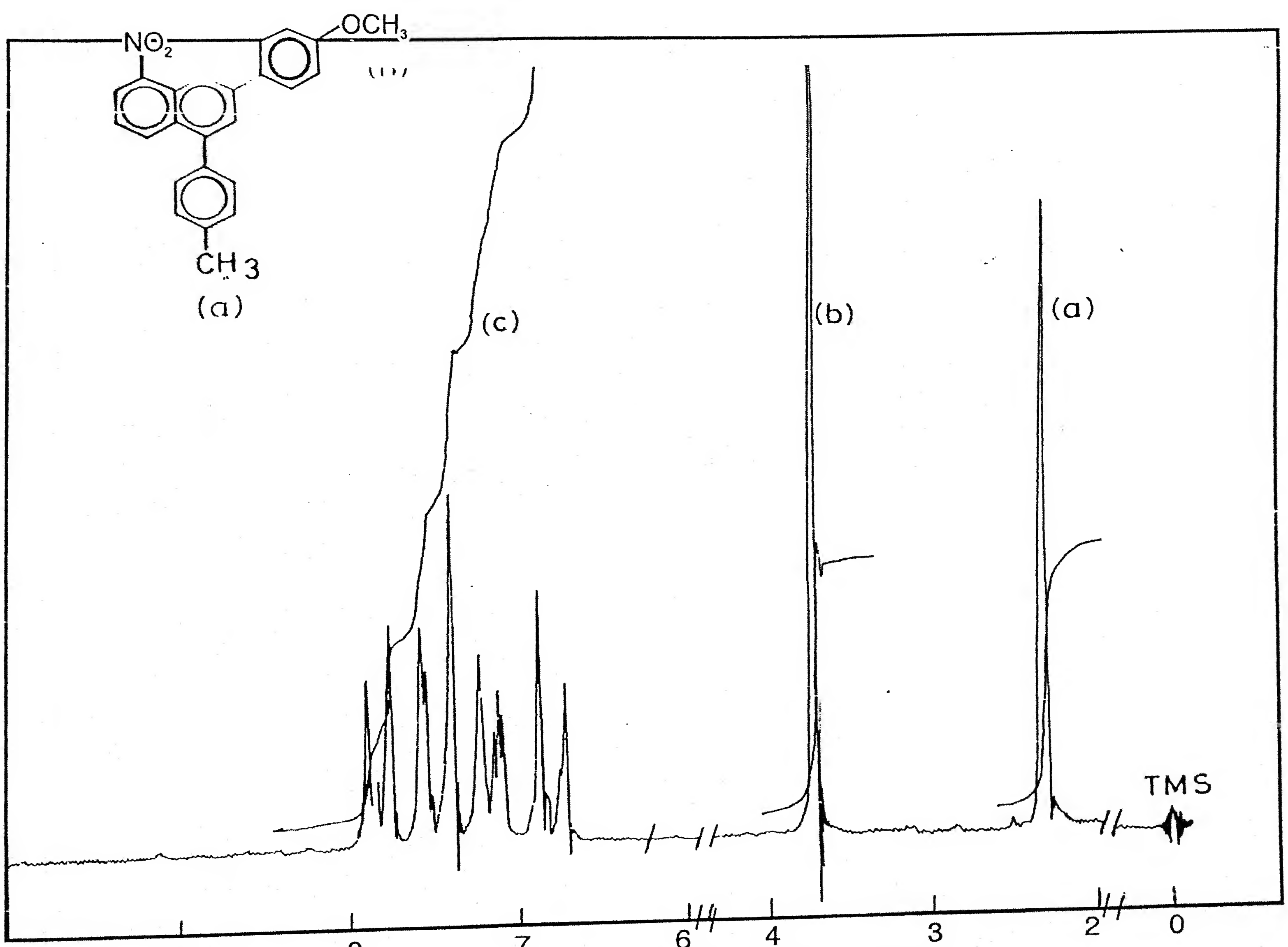

Fig. V 2. NMR spectrum of compound (17g)

Table V.1 Physical Properties of 1,3-nitro naphthalenes (17a-m)

Compd.	Ar^1	Ar^2	Yield %	M.P. ^0C	Analysis found/(Calcd)% C	H	N
1	2	3	4	5	6	7	8
17 a	C_6H_5	C_6H_5	60	96-98	81.25	4.054	.36
					(81.20)	(4.61)	(4.30)
17 a	C_6H_5	C_6H_5	60	96-98	81.25	4.05	
					(81.20)	(4.61)	(4.30)
b	C_6H_5	$4\text{-}CH_3C_6H_4$	65	166-68	81.98	5.054	.20
					(81.98)	(5,05)	(4.20)
C	C_6H_5	$4\text{-}CH_3OC_6H_4$	60	124-26	77.60	4.723	.16
					(77.60)	(4.72)	(3.16)
d	C_6H_5	$4\text{-}Cl.C_6H_4$	75	134-36	73.95	3.823	.68
					(73.95)	(3.82)	(3.68)
e	C_6H_5	$3,4\text{-}O_2CH_2$	65	136-38	74.71	4.103	.78
					(74.80)	(4.06)	3.79)
f	$4\text{-}CH_3C_6H_4$	C_6H_5	50	158-60	81.92	5.094	.18
					(81.89)	(5.01)	(4.12)
g	$4\text{-}CH_3\text{-}$ C_6H_4	$4\text{-}CH_3OC_6H_4$	60	110-12	78.16	5.183	.70
					(78.10)	(5.14)	3.79)
h	$4\text{-}ClC_6H_4$	$4\text{-}NO_2C_6H_4$	`65	136-40	66.15	3.207	.07
					(66.15)	(3.25)	(7.00)
i-	$C_{10}H_7$	C_6H_5	55	178-80	83.08	4.483	.66
					(83.20)	(4.55)	(3.73)
J	$2\text{-}C_{10}H_7$	$4\text{-}ClC_6H_4$	65	168-70	76.10	3,983	.48

Cont. Table V.1

1	2	3	4	5	6	7	8
					(76.19)	(3.90)	(3.41)
k	2-$C_{10}H_7$	3-$CH_3C_6H_4$	45	198-98	82.61	5.253	.75
					(82.53)	(5.29)	(3.70)
l	4-C_6H_5 C6H4	C_6H_5	55	144-46	83.70	4.773	.58
					(8379)	(4.73)	(3.49)
m	2-C_4H_3S	4-$CH_3OC_6H_4$	55	188-90	79.70	5.014	.15
					(79.74)	(5.00)	(4.11)

Table V.2 Spectral properties of 1,3-diaryl-5-nitronaphthalenes (17 a-m)

Compd.	NMR ($CDCl_3$) data			IR (KBR) data cm^{-1}		
	δ (PPm)	No.of Protons	Assignment of protons	νC=C	φC–H	νC–NO_2
1	2	3	4	5	6	7
17 a	-	-	-	1600	995	1490, 1330
b	2.45	3H	CH3	1605	992	1495, 1332
	6.95-8.25,m	14H	ArH			
c	3.90,s	3H	OCH_3	1598	988	1500,1340
	6.80-8.25,m	14H	ArH			
d	-	-	-	1610	985	1505,1335
e	6.08,s	2H	OCH_2O_2	1595	990	1500,1320
	6.70-8.20,m	13H	ArH			
f	2.40,s	3H	CH_3	1608	996	1520,1335
	6.85-8.15,m	14H	ArH			
g	2.30,s	3H		1608	994	1515,1340
	3.75,s	3H	OCH_3			
	6.80-8.25,m	13H	ArH			
h	-	-	-	1615	998	1528,1330
i	-	-	-	1610	998	1525,1338
j	-	-	-	1615	996	1525,1330
k	2.33,s	3H	CH_3	1628	988	1510,1340
	7,13-8.35,m	16H	ArH			
l	-	-	-	1630	998	1525,1335
m	3.85,s	3H	OCH_3	1625	998	1535,1328
		6.80-7.95	12H	ArH		

* s= singlet, m=multiplet, υ=streching vibration. φ=out o plances deformation

Chapter-VI

Chapter -VI

SYNTHESIS OF SOME NEW 2,4,6-TRISUBSTITUTED PHENYL PYRIMIDINES USING 4-NITRO AND 4- FLUORO-PHENACYLDIMETHYLSULFONIUM BROMIDES WITH AROMATIC ALDEHYDES.

VI.1 Abstract

4- Nitrophenacyldimethylsulfonium bromide and 4-fluorophenacyldimethylsulfonium bromide have been prepared by the reaction of dimethylsulfide with 4- substitutedphenacyl bromide in benzene at reflux temperature under nitrogen atmosphere. These sulfonium salts on treatment with NaOH gave 4- nitrophenacy-lidenedimethylsulfurane and 4-fluorophenacylidenedimethyl-sulfurane.The reaction of these sulfonium salts and sulfuranes with various aromatic aldehydes is carried out in presence of ammonium acetate and acetic acid at reflux in an atmosphere of nitrogen to geve 2,4,6,- triarylpyrimidines in 35-80% yields. Ammonium acetate in acetic acid was used as aza cyclization agent. The structures of new pyrimidines were confirmed on the basis of IR and NMR spectral data.

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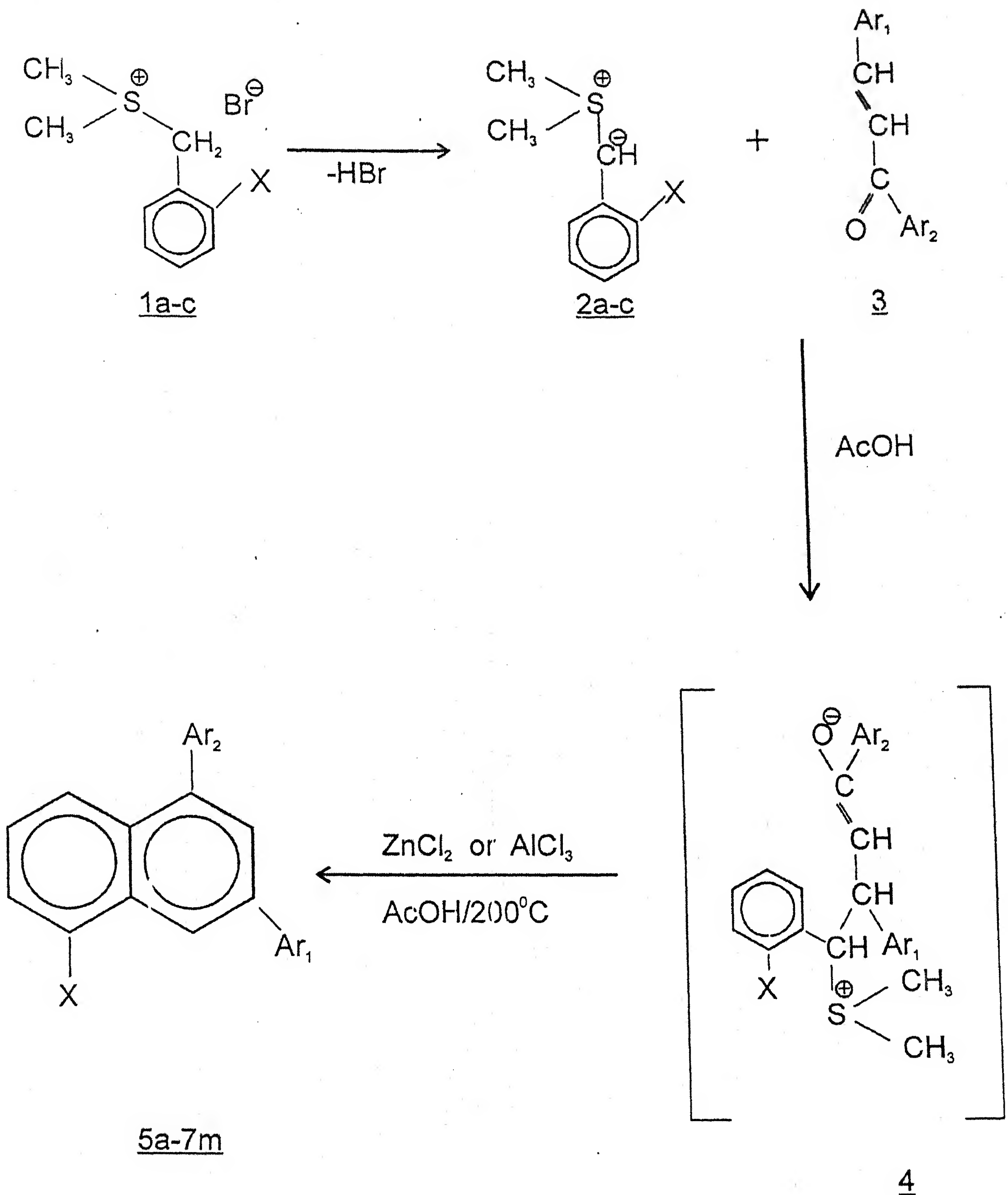
* A part of this work has been published in J. Ind. Chem. Soc. **84**, 299-303 (2007)

VI.2 Introduction

Pyridinium, phosphonium, arsonium and isoquinolinium ylides have gained considerable importance in the synthesis of acyclic, cyclic and heteocyclic compounds[1-7]. As reported earlier sulfonium salts and sulfuranes are also better potential reagents than corresponding salts and ylides of Vth group elemen:s for synthesis of cyclic and heterocyclic system.[8-15] Krohnke[16] first time reported in a single reaction involving condensation of phenacylpyridinium bromide with 4- nitrobenaldehyde to yield 2,4- di (4-nitrophenyl)- 6- pheylpyrimidine. The detailed experimental conditions were not reported earlier[16]. As in the several cases sulfonium and pyridinium ylide follow the similar course in several case of reactions[1-17]. Hence, further extensions of reaction sulfonium ylides leading to the pyrimidine nucleus seems to be pertinent with a view to test the domain of applicability of sulfonium ylides. In the present investigation 4- nitrophenacyldimethyl-sulfonium bromide and 4- fluorophenacyldimethylsul fonium bromide as well as their corresponding sulfuranes have been coupled with a wide range of aromatic aldehydes in the presence of ammonium acetate and acetic acid at reflux temperature leading to ring closure to form pvrimiain nucleus.

SCHEME -VII.1


CH3
CH3
S
Br
CH2
X
-HBr
1a-c
CH3
CH3
S
CH
X
2a-c
+
Ar1
CH
CH
C
O
Ar2
3
AcOH
O
Ar2
C
CH
CH
CH
Ar1
X
S
CH3
CH3
4
ZnCl2 or AlCl3
AcOH/200°C
Ar2
Ar1
X
5a-7m

VII.3 Results and Discussion

Reaction of dimethylsulfide with 4-nitrophenacyl bromide and 4-fluorophenacyl bromide in benzene at reflux temperature gave 4-nitrophenacyl bromide (la) and 4-fluorophenacyldimethylsulfonium bromide (1b) in fair to good yields. The structure of sulfonium salts (1a-b) were confirmed by comparision of melting points of salts with thos: reported in the literature[15-17] and by spectral data. The IR spectra of salts (1a-b) showed a characte:istic absorption band due to C-O stretching vibrations in the region 1670-1690 cm^{-1} for carbonyl group. The diagnostic absorption bands in the region 3300-3000 cm-1 were observed due to C-H stretching vibrations of methylene group attached to sulfur atom[18-19]

The treatment of these salts (1a-b) which are highly unstable the reaction was therefore carried out by generating the ylide intermediates (2a-b) ***'in situ'*** from the corresponding salts (1a-b).,

Heating the miture of sulfonium salts (1a-b) with substituted benzaldehyde (3a-1) in presence of ammonium acetate and glacial acetic acid at reflux tempetature gave 2,4,6-triarylpyrimid-ines (5a-1, 6a-1) in 35-80%yields (Scheme-VI.1)

Further attempts were made to synthesize symmetrical pyrimidines having identicak substituengs at 2,4,6-positions. For this purpose 4-nitrophenacyldimethylsulfonium bromide (1a) with 4-nitrobenzaldehyde and 4-fluorophenacyldimethylsulfonium bromide (1b) with

4- nitrobenzaldehyde fluorobenzaldehydewere heated in a mixture of ammonium acetate and glacial acetic acid to give corresponding symmetrical pyrimidines viz.2.4.6-tri-(4-nitrophenyl) pyrimidine (51) and 2,4,6,-tri- (4-fluorophenyl) pyrimidine (6g) respectively in 60% and 65% yields.(Scheme-VI.2)

The reaction takes place through Mannich type reaction. The methylene group of salt (1a-b) with aromatic aldehydes (3a-1) in presence of ammonium acetate forms Mannich base sulfonium salt (4a) with ammonia. This sulfonium salt (4a) which, in turn, undergoes condensation with another molecule of benzaldehyde in presence of ammonia to form sulfonium salt intermediate (4b). The later, undergoes elimination of dimethylsulfonium hydrobromide to form 2,4,6-triaryl pyrimidines (5a-1,6a-1).

A number of 2,4,6-triaryl pyrimidine (5a-1) and (6a-1) synthesized by the above route are new and listed in table VI.1. All the pyrimidines gave satisfactory elemental and spectral analyses. The IR spectral data showed (Table VI.2) characteristic absorption bands in the region $3100cm^{-1}$- $3000cm^{-1}$ which were assigned due to C-H stretching mode of pyrimidine ring. The bands in the region 1600-$1500cm^{-1}$ were due to interaction between C=C and C=N vibrations of the pyrimidine ring. The NMR spectra (Table VI.3) of pyrimidines showed pyrimidyl protons at C5-H in the range δ6.60–6.80 and aromatic protons at δ6.60–8.40.

VI.4 Experimental

Starting Material

All the reagents were obtained from commercial sources (E.Merck, BDH,SISCO etc.) Starting materisla viz. 4-nitrophenacyl bromide and 4-fluorophenacyl bromide were prepared according to the procedure reported in literature[20].

PREPARATION OF 4-SUBSTITUTED PHENACYLDIMETHYL SULFONIUM BROMIDE (1a-b) :

A solution of 100m mole of 4-nitrophenacyl bromide and 100m mole of dimethyl sulfide in 100ml of anhydrous acetone was stirred for 6-8 hrs. at room temperature in an atmosphere of nitrogen gave solid mass which was filtered, washed twice with acetone and crystallized from benzene pet. Ether as detailed below.

4-Nitrophenacyldimethyl sulfonium bromide (1a), yellow coloured micro crystals m,p. 150-152^{0}C (Lit.[15] m.p. 152-154^{0}C).

IR data (KBr) υ_{max} cm^{-1} : 1680 Cm^{-1} (υC=O) 1570,1330Cm^{-1}(υC-NO_2)

NMR ($CDCI_3$) δ(ppm) : δ3.30 (s,6H.di CH_3) : δ5.50 (s,2H,CH_2) δ7.30-7.90 (m,4H,Ar-H)

4-Fluorophenacyldimethylsulfomnium bromide (1b), white colourless microcrystals m.p.140-142^{0}C (Lit.[17] m.p. 142-144^{0}C).

IR data (KBr) υ_{max} cm^{-1} : 3100 (ArH), 1675cm^{-1} (δC=O)

NMR ($CDCI_3$) (δppm) : δ3.26 (s,6H,di CH_3) : δ8.45 (s,2H,CH_2) : δ 7.25–7.85 (m,4H,ArH).

PREPARATION OF 2,4,6-TRIARYLPYRIMIDINES (5a-1,6a-1)

General procedure

A mixture of 3 mmole 4-substituted phenacyldimethylsulfonium bromide (1a-b) and 6 mmole of aromatic aldehyde (3) and 3gm of ammonium acetate in 50ml of glacial acetic acid was stirred at room temperature. The mixture was then poured in ice cold water (50ml) which was constantly stirred. The solid mass was precipitated, filtered and washed twice with water and then with methanol and dried. The product , was chromatographed over neutral alumina and chlorform : pet. ether as mobile solvent gave crystalline products which were recrystalised from suitable solvent to give 2,4,6-triarylpyrimidine (5a-1) & (6a-1) in good yields as computed in table VI.1.

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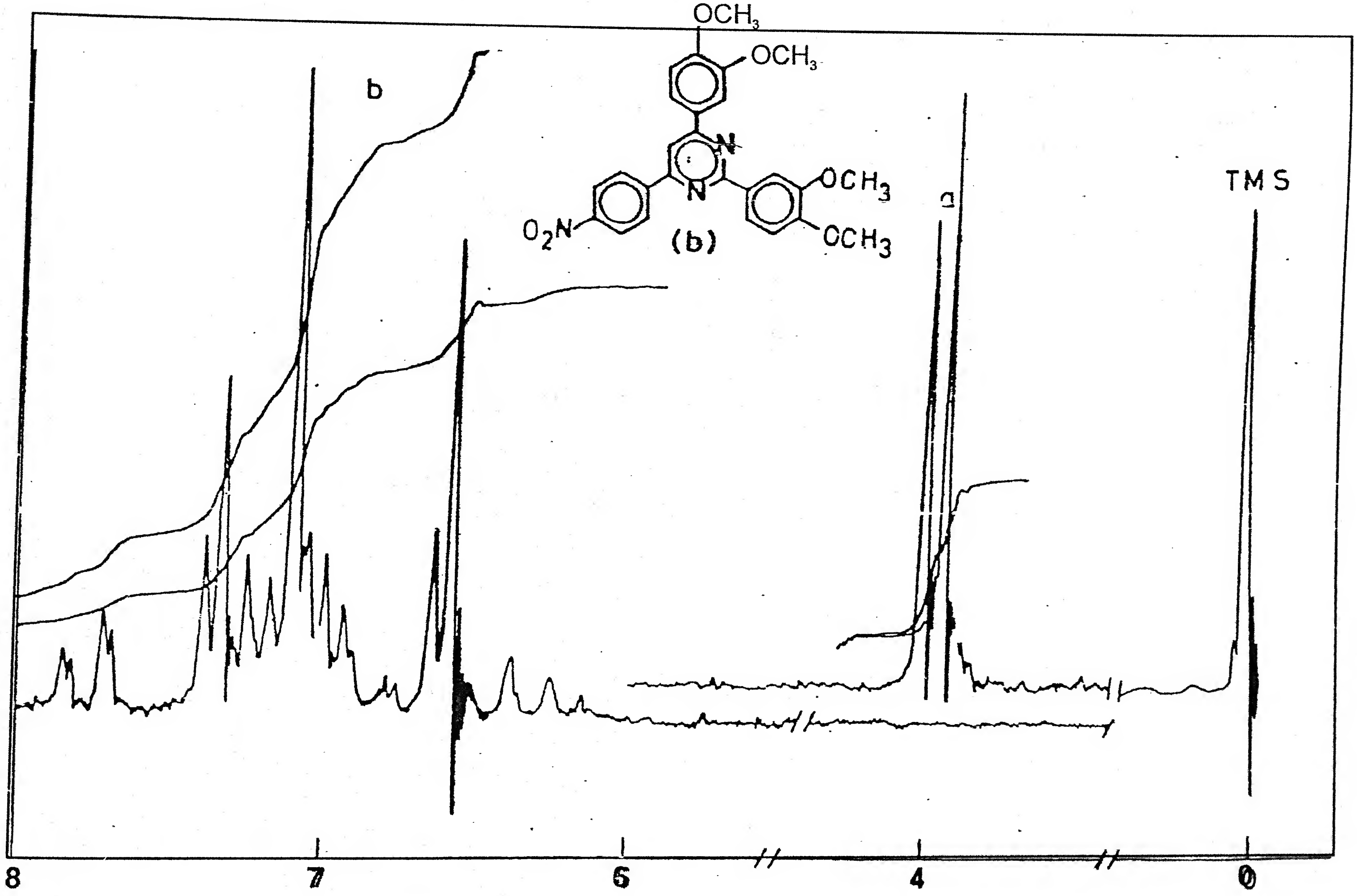

Fig. VI 1. NMR spectrum of compound (5h)

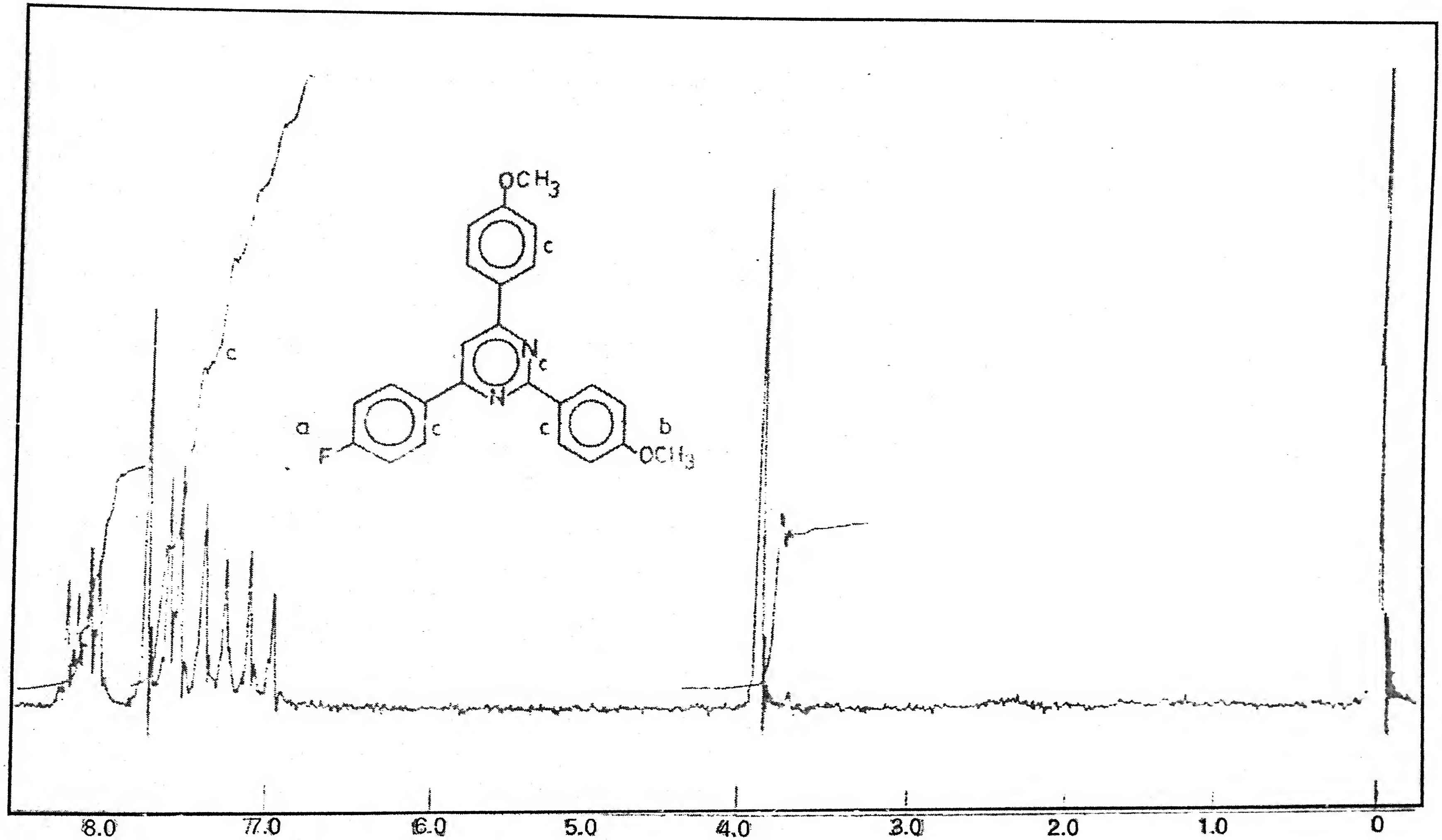

Fig VI.2 : NMR Spectrum of compound (6d)

TABLE.VI.1. Physical Properties of 2,4,6,-Triarylpyridines (5a-1, 6a-1)

Compoound	X	Y	Yield %	M.P. 0C	Recrystn. solvent	Analysis found (Calcd.) % C	H	N
1	2	3	4	5	6	7	8	9
5a	4-NO^2	H	45	110-12	A	74.02 (74.05)	4.35 (4.37)	12.20 (12.24)
b	4-NO^2	4-CH_3	40	96-98	B	75.61 (75.59)	4.93 (4.98)	11.04 (11.02)
c	4.NO^2	4-$N(CH_3)_2$	45	120-22	A	71.03 (71.07)	5.67 (4.98)	15.99 (15.95)
d	4-NO^2	4-OCH_3	60	128-30	C	69.70 (69.73)	4.62 (4.60)	10.14 (10.07)
e	4-NO^2	4-Cl	65	78-80	A	62.54 (62.56)	3.04 (3.08)	10.07 (10.05)
f	4-NO^2	4-Br	55	86-98	B	55.76 (55.81)	2.71 (2.75)	8.82 (8.88)
g	4-NO^2	4-F	65	110-12	C	67.80 (67.87)	3.36 (3.34)	9.27 (9.26)
h	4-NO^2	3,4dl(OCH_3)	48	122-24	A	70.40 (70.59)	5.68 (5.64)	9.42 (9.48)
i	4-NO^2	4-NO_2	80	132-34	C	59.55 (59.59)	2.90 (2.93)	15.82 (15.80)

Contd. Table.1.

1	2	3	4	5	6	7	8	9
6a	4-F	H	48	98-10	D	80.92 (80.98)	4.62 (4.60)	11.62 (11.64)
b	4-F	4-CH_3	45	112-14	B	81.34 (75.59)	5.37 (4.98)	7.92 (11.02)
c	4-F	4-$N(CH_3)_2$	41	124-26	C	75.70 (75.72)	6.06 (6.07)	13.52 (13.59)
d	4-F	4-OCH_3	42	130-320	A	78.42 (78.47)	5.15 (5.17)	7.64 (7.62)
e	4-F	4-Cl	50	76-78	C	66.80 (66.84)	3.26 (3.29)	7.05 (5.79)
f	4-F	4-Br	55	88-90	A	57.80 (57.85)	2.67 (2.69)	5.75 (5.79)
g	4-F	4-F	60	108-10	B	72.90 (72.93)	3.52 (3.59)	7.70 (7.73)
h	4-F	3,4-dl(OCH_3)	50	124-26	A	69.94 (69.99)	5.13 (5.15)	6.24 (6.28)
i	4-F	4-NO_2	45	128-30	C	63.42 (63.46)	3.10 (3.12)	13.42 (13.46)

A = $CH_3OH : CHCl_3$ (1:3) B = $C_6H_6 : CHCl_3$ (1:3) C = $C_5H_5N : CH_3OH$

Table VI.2. IR Data (KBr) cm-1 2,4,6- Triarylpyrimidines (5a-i, 6a-i)

Compound	IR Data (KBr) cm^{-1}				
	υ C-H	υ C=C	υ C-N	∅ C-H	υ C-nNO$_2$
5a	3110	1605	1510	995	1555, 1325
b	3085	1615	1525	990	1575, 1330
c	3105	1605	1510	995	1580, 1335
d	3115	1610	1520	992	1585, 1335
e	3060	1608	1505	990	1580, 1340
f	3110	1595	1500	1000	1575, 1320
g	3080	1598	1505	1005	1570, 1325
h	3108	1605	1510	1000	1580, 1330
i	3070	1610	1510	1005	1575, 1320
6a	3090	1600	1505	998	
b	3105	1605	1510	1005	
c	3100	1615	1500	992	
d	3065	1598	1500	1000	
e	3080	1605	1510	1010	
f	3100	1615	1505	992	
g	3105	1614	1505	995	
h	3080	1600	1500	998	
i	3095	1608	1505	990	

υ = Stretching vibrations :

∅ = Out of plane deformation of hydrogen attached to aromatic nucleus. (5a-1, 6a-1)

Table VI. 3. NMR ($CDCl_3$) Data of 2,4,6- Triarylpyrimidines (5a-i, 6a-i)

Compound	δ (ppm)	No.of protons	Assignment of protons
1	2	3	4
5a	6.65, s	1H	PyH (C_5-H)
	6.85-6.88, m	14H	Ar-H
b	6.25, s	1H	PyH (C_5-H)
	2.35, s	6H	di CH_3
	6.95-8.20, m	12H	ArH
c	6.65, s	1H	Pyh (C_5-H)
	3.95, s	12H	di (OCH_3)
	6.75-7.85, m	12H	Ar-H
d	6.66, s	1H	PyH (C_5-H)
	3.85, s	6H	di (OCH_3)
	6.95-8.35, m	12H	ArH
e	6.78, s	1H	PyH (C_5-H)
	7.0-8.25, m	12H	Ar-H
f	5.80, s	1H	PyH (C_5-H)
	6.95-8.20, m	12H	ArH
g	6.75, s	1H	Phy(C_5-H)
	7.10-8.35, m	12H	Ar-H
h	6.65, s	1H	PyH (C_5-H)
	3.95, d, (J=6H_z)	12H	di (3,4-di OCH_3)
	6.85-7.85, m	10H	ArH
i	6.75, s	1H	PyH (C_5-H)
	7.05-8.35, m	12H	ArH

Contd. Table 3.

1	2	3	4
6a	6.60, s	1H	PyH (C_5-H)
	6.75-7.95, m	14H	ArH
b	6.65, s	1H	PyH (C_5-H)
	2.50, s	6H	di CH_3
	6.85-8.15, m	12H	ArH
c	6.70, s	1H	Pyh (C_5-H)
	2.95, s	12H	di (OCH_3)
	6.85-7.15, m	12H	ArH
d	6.60, s	1H	PyH (C_5-H)
	3.95, s	6H	di (OCH_3)
	6.95-8.35, m	12H	ArH
e	6.75, s	1H	PyH (C_5-H)
	7.05-8.35, m	12H	ArH
f	6.80, s	1H	PyH (C_5-H)
	7.15-8.45, m	12H	ArH
g	6.85, s	1H	Phy(C_5-H)
	7.10-8.35, m	12H	ArH
h	6.65, s	1H	PyH (C_5-H)
	3.85, d (J=6H_z)	12H	di (3,4-di OCH_3)
	6.95-8.28, m	10H	ArH
i	6.70, s	1H	PyH (C_5-H)
	7.10-8.35, m	12H	ArH

s = singlet m = multiplet d = doublet

Chapter-VII

SYNTEHSIS OF 1,3,5-TRISUBSTITUTED NAPHTH-ALENES USING NON STABILIZED π–SULFURANES : REACTION OF O-SUBSTITUTED BENZYLDIMETH - YLSULFONIUM BROMIDES WITH α,β-UNSATUR- ATED KETONES.*

VII.1 Abstract

O-substitutedbenzyldimethylsulfonium bromides have been prepared by the reaction of o-substitutedbenzyl bromide with dimethyl sulfide in benzene in an atmosphere of nitrogen at reflux temperature in good yields. These sulfonium salts on reaction with base generated corresponding o-substituted benzylidenedimethyl sulfuranes *'in situ'*. The reaction of these salts or sulfuranes with a wide range of substituted benzylideneacetophenones in presence of anhyd. $AlCl_3$ or $ZnCl_2$ in mixture of ammonium acetate and acetic acid gave 1,3,5-triarylnaphthalenes in good yields. Aluminium choloride or zinc chloride in acetic acid is used as cyclisation agent. The structures of naphtalenes were confirmed by elemental analysis, IR and NMR spectral data.

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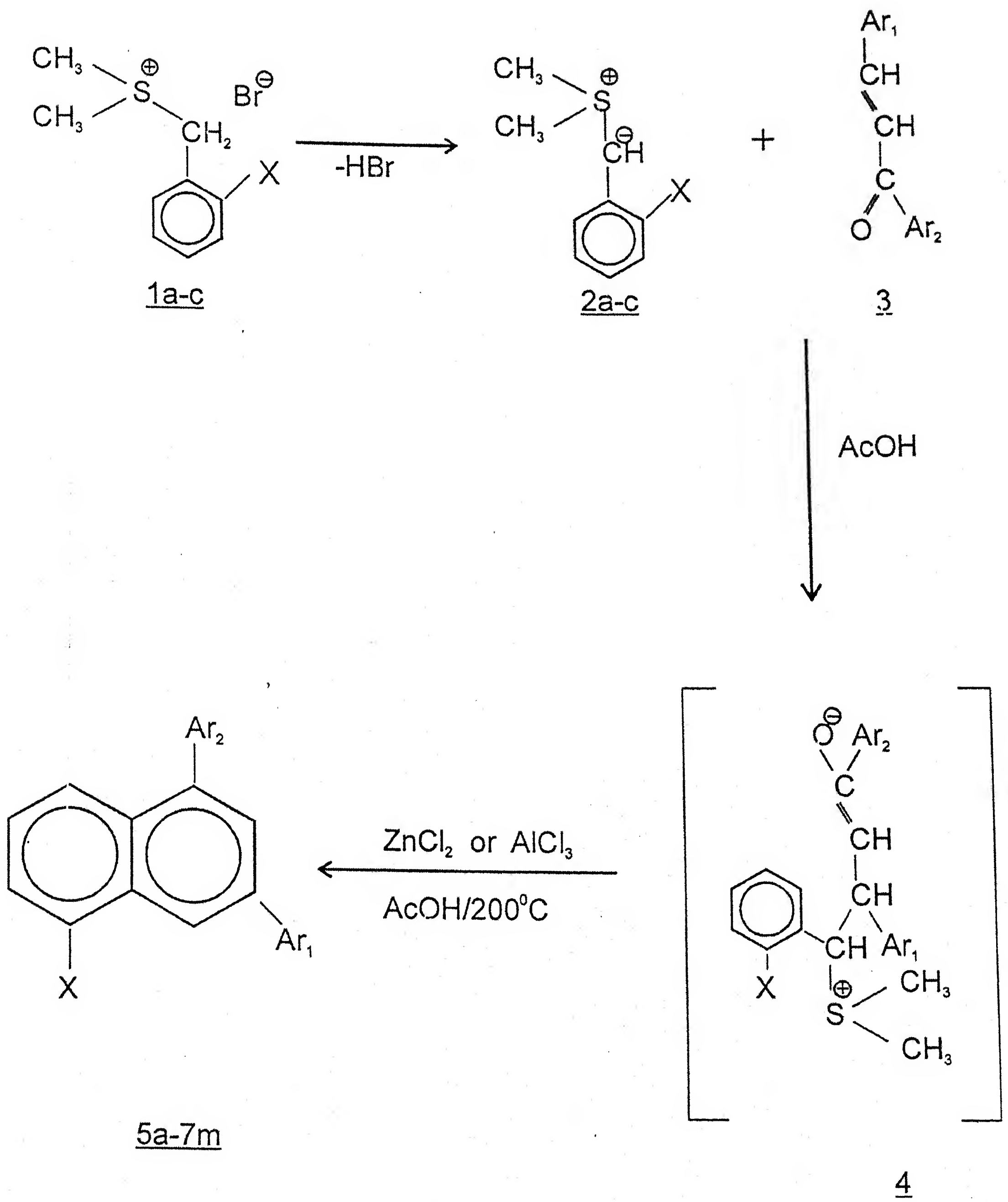
* A part of this work has been published in Proc. Nat. Acad. Sc. (Sec.A) III Issue (2008)

VII.2 Introduction

Pyridinium, phosphonium and arsonium ylides have gained considerable importance in the synthesis of acyclic, cyclic and heterocyclic compounds[1-7]. Noteworthy in this regards, are the synthesis of pyridines[1,2], indoles[3], tetrazines[4], cinnolines[5], epoxides[6,7], cyclopropanes[7], azaridines[7], and several others heterocycles. As reported earlier sulfonium salts and sulfurance are better potential reagents than corresponding ylides of Vth group elements for the synthesis of heterocycles[1-7]. Earlier a convenient route was first reported by Krohnke's et.al[8] for the synthesis of diarylnaphthalene derivative which involved the condensation of benzylpyridinium bromide with benzalacetophenone in presence of $ZnCl_2$ in acetic acid. Krohnke's method[8] proved better method for synthesis of naphthalenes because it involved single step and gave better yields of product. Later on Tewari & Gupta et al[9,10] also extended the reaction of pyridinium ylides and reported the detailed experimental conditions for the preparation of 1,3-diarylnaphthalenes. Prompted from this it was, therefore, thought worthwhile to investigate an alternative route for the synthesis of naphthalene derivatives which involved the reaction of sulfonium salts and ylides with α,β-unsaturated ketones with a view to explore synthetic applicability and to compare the course of sulfonium ylides with the ylides of Vth group elements.

SCHEME -VII.1



CH3
CH3
S
Br
CH2
X
1a-c
-HBr
CH3
CH3
S
CH
X
2a-c
+
Ar1
CH
CH
C
O
Ar2
3
AcOH
O
Ar2
C
CH
CH
CH
Ar1
X
S
CH3
CH3
4
ZnCl2 or AlCl3
AcOH/200°C
Ar2
Ar1
X
5a-7m

VII.3 Results and Discussion

The reaction of o-substitutedbenzyl bromide with dimethyl sulfide in benzene at reflux temperature under nitrogen atmosphere gave o-substitutedbenzyldimethylsulfonium bromides (1a-c). The structures of these sulfonium salts (1a-c) on the basis of IR and NMR data[11-12].

The reactions of these salts (1a-c) were carried out with a wide range of α, β-unsaturated carbonyl compounds in presence of anhydrous $AlCl_3$ or $ZnCl_2$ in presence of mixture of sodium acetate and acetic acid at 200°C to give 1,3 diaryl-5-substitutednaphthalenes (5a-7m) in 50-75% yields. It was however observed that the yields of the naphthalenes were dependent upon the nature of subtituents attached to sulfonium salts (1a-c) as well as on α,β-unsaturated ketones. The reactivity of salt (1c) was lower than (1a-b) because of –I effect of NO_2 group which stabilized carbanian formation Hence, salts (1c) afforded lower yields of naphthalene derivatives than the salts (1a-b).

The reaction seems to proceed via the intermediacy of betaine type derivatives (4) which is formed by a nucleophilic attack of the ylide carbanion (2a-c) generated in situ by dehydrohalogenation of salts (1a-c), on β-carbon of α,β-unsaturated ketones (3), Betaine (4) then undergoes cyclisation in presence of anhydrous $ZnCl_2$ or $AlCl_3$ used as cyclization agent to afford naphthalenes (5a-7m) (Scheme-VII.1). The course of reaction is similar to pyridinium ylides.[8-10]

All the naphthalenes gave satisfactory elemental analysis. The IR spectral data (table VII 2) of naphthalenes showed a double absorption maxima in the region 1630-1620cm^{-1} which were assigned to the stretching vibrations of crbon carbon double bond. The strong bands in the region 900-850cm^{-1} were diagnostic absorption of polynuclear aromatics. The nitrogroups of the products showed a strong symmetrical stretching band at 1350-1330cm^{-1}. The NMR spectral data of compounds in gernal exhibited aromatic multiplet in the range of δ6.50-8.50, methyl protons at δ2.25-2.30 and methoxy protons at δ3.75-3.80

VII. 4 Experimental

Starting Material

All the reagents obtained from commercial sources (E-Merck, BDH, Fluka &SISCO) Melting points were recorded on Gallen Kamp apparatus and are uncorrected IR spectra were recoreded on Perkin-Elmer Infracord Spectrophotometer using KBr phase. Varain A-60 and Varain A-100 spectrometer were used to record NMR spectra using TMS as an internal standard.

4.1 Preparation of o-substituted benzyldimethylsulfonium bromide (1a-c)

A solution of dimethylsulfide (50 mmol) and o-substitued benzyl bormide (50 mmol) in 50ml of anhydrous benzene was allowed to reflux on water bath for 4-6 hrs. A solid mass precipitated which was

filttered, dried and recrystallized twice from chloroform: n hexane (1:2) to give sulfonium salts as detailed below

1. o-Chlorobenzyldimethylsulfonium bromide (1a) in 80% yields, m.p. 150-151°C (lit[11] mp. 150°-152°C).
2. o-Bromobenzyldimethylsulfonium bromide (1b) in 75% yields, m.p. 142-144°C (lit[11] m.p. 150°-152°C).
3. o-Nitrobenzyldimethylsulfonium bromide (1c) in 90% yields, m.p. 158-160°C (lit[12] m.p. 155-157°C)

4.2 Preparation of 1,3-Diary1-5-Substitutednaphthalenes (5a-7m)

General procedure

A mixture of sulfonium salts (1a-c) (3mmol) and α, β-unsaturated ketones (3) (3mmol) was stirred at 200°C in presence of anhyd. $ZnCl_2$ (3.0gm) in 40ml glacial acetic acid and ammonium acetate (3.0gm) for 6-9 hours under nitrogen atmosphere. The reaction mixture after keeping overnight at room temperature, ice cold water (20-30ml) was then added to precipitate a solid mass. The solid mass so obtained was sperated by filtration, washed with water and dried. The product was subjected to column chromatography using neutral alumina as adsorbent and chloroform as mobile solvent. The product was recrystalised from suitable solvent to give good yields of the titled compounds (5a-7a). (table VII.1). The NMR and IR data of products have been tabulated in table VII 2-3.

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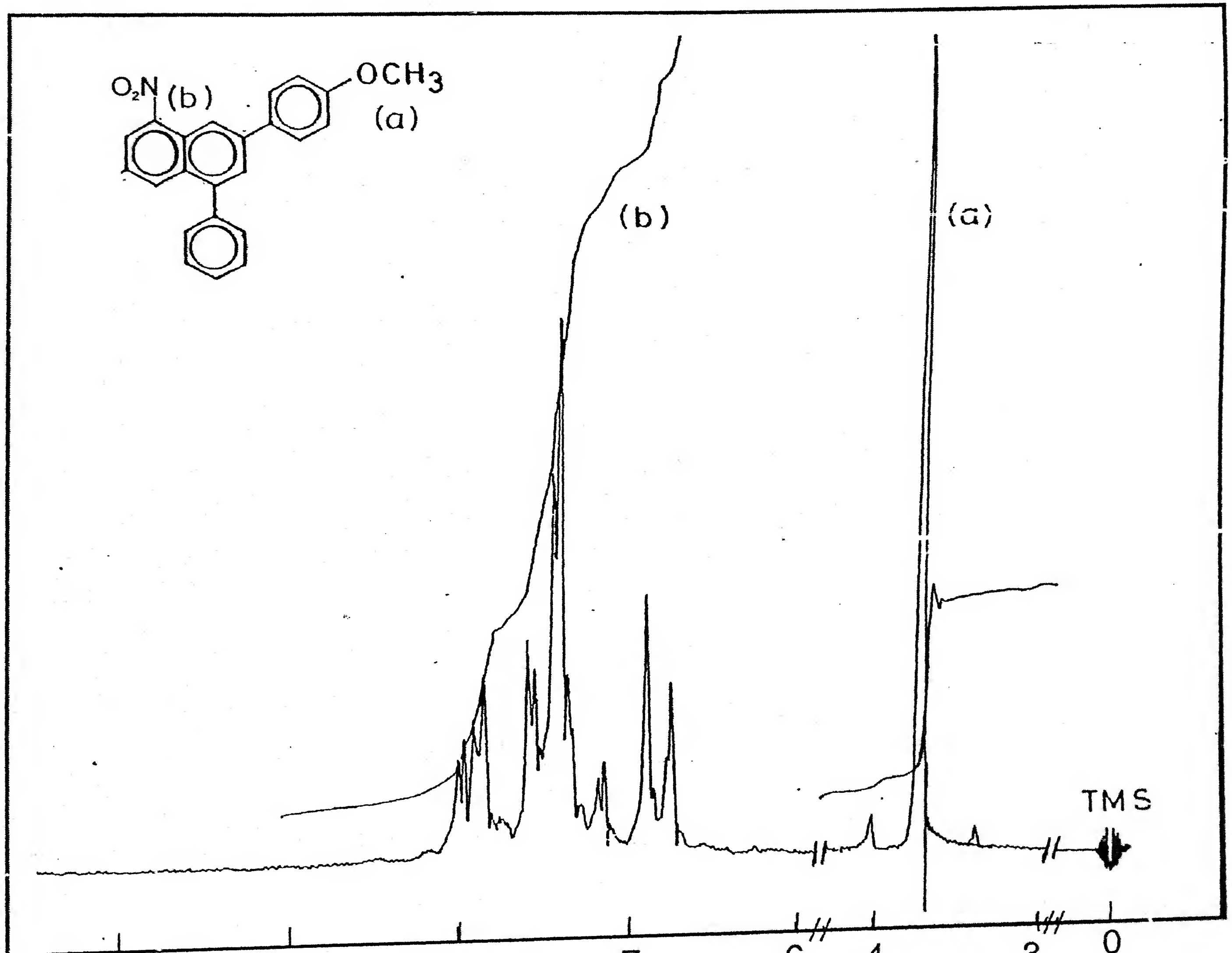

Fig. VII 1. NMR spectrum of compound (7c)

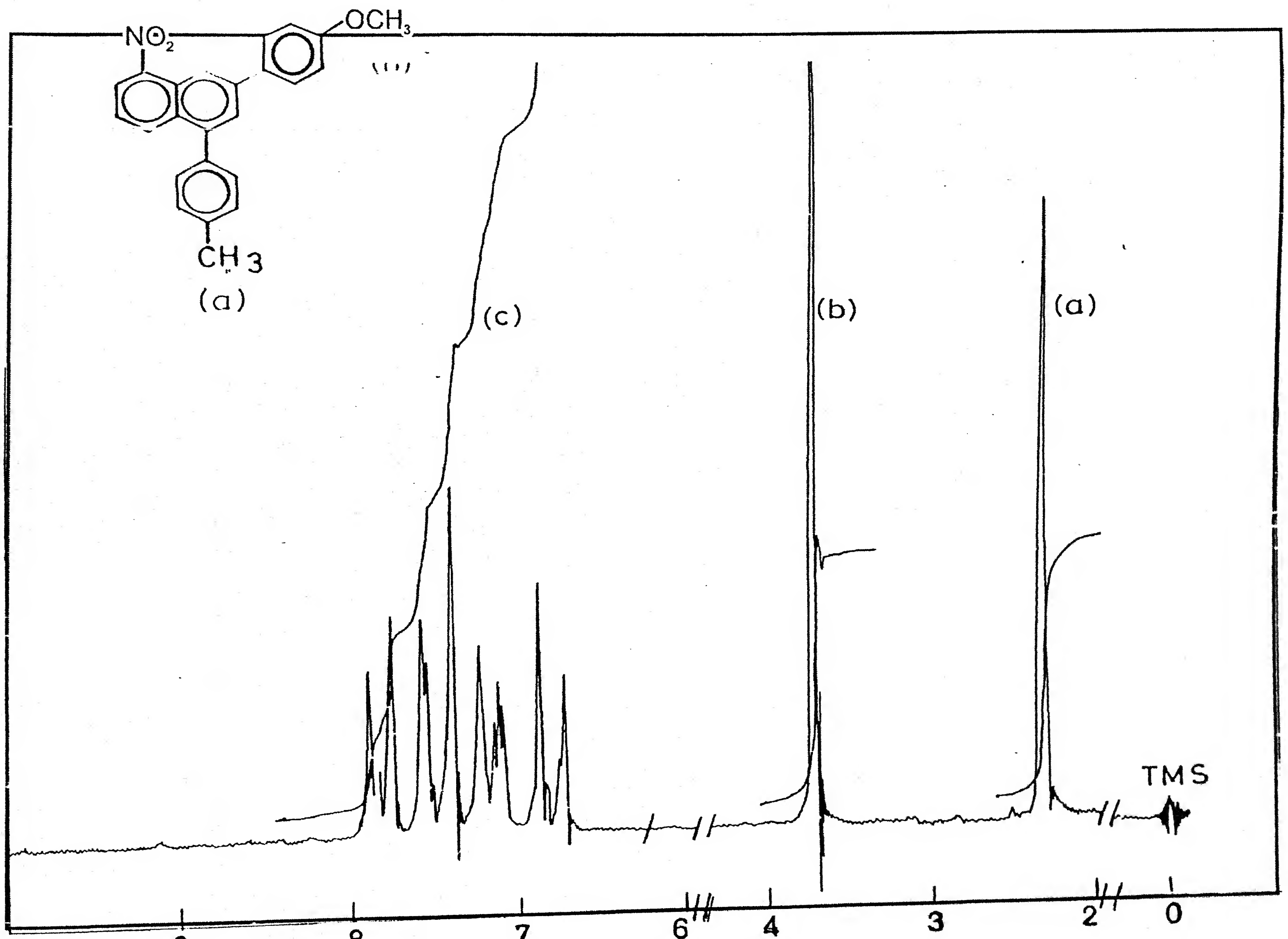

Fig. VII 2. NMR spectrum of compound (7g)

TABLE VII.1 – PHYSICAL PROPERTIES OF NAPHTHALENE DERIVATIVES (5A-7M)

Compd	X	Ar_1	Ar_2	Yield %	M.P. °C	Lit.[6] M.P. °C	Recry-stn. solvent	Anal. Data found/(Calcd.)% C	H
1	2	3	4	5	6	7	8	9	10
5a	Cl	C_6H_5	C_6H_5	60	92-94	94-96	B	83.82 (83.94)	4.83 (4.77)
b	Cl	C_6H_5	$4-CH_3C_6H_4$	60	109-111	108-110	C	84.04 (84.02)	5.14 (5.18)
c	Cl	C6H5	$4-CH_3OC_6H_4$	64	124-126	125-127	A	80.18 (80.12)	4.82 (4.93)
d	Cl	C_6H_5	$4-ClC_6H_4$	56	108-110	110-112	C	75.61 (75.42)	4.07 (4.10)
e	Cl	C_6H_5	$3,4-O_2CH_2C_6H_3$	65	134-136	133-135	C	77.38 (74.42)	3.70 (3.65)
f	Cl	$4-CH_3C_6H_4$	C_6H_5	67	120-121	121-122	A	84.05 (84.02)	5.06 (5.14)
g	Cl	$4-CH_3C_6H_4$	$4-CH_3OC_6H_4$	62	96-98	95-97	B	80.28 (80.33)	5.32 (5.14)

Contd. Table VII.1

1	2	3	4	5	6	7	8	9	10
h	Cl	4-ClC_6H_4	4-$NO_2C_6H_4$	55	192-193	190-191	B	69.90 (69.84)	3.50 (5.44)
i	Cl	2-$C_{10}H_7$	C_6H_5	60	170-172	170-172	C	85.57 (85.60)	4.59 (4.66)
j	Cl	2-$C_{10}H_7$	4-Cl.C_6H_4	62	173-174	171-174	A	78.25 (78.20)	4.07 (4.01)
k	Cl	1-$C_{10}H_7$	3-$CH_3C_6H_4$	67	189-191	190-192	B	85.53 (85.60)	5.08 (5.02)
l	Cl	4-$C_6H_5C_6H_4$	C_6H_5	65	162-164	160-162	C	86.07 (86.04)	4.78 (4.87)
m	Cl	C_6H_5	4-$CH_3O.C_6H_5$	72	173-174	172-173	A	71.80 (71.90)	4.33 (4.28)
6a	Br	C_6H_5	C_6H_5	68	92-93	94-96	B	73.40 (73.53)	4.45 (4.56)
b	Br	C_6H_5	4-$CH_3C_6H_4$	70	113-115	112-114	A	73.90 (73.95)	4.50 (4.56)
c	Br	C_6H_5	4-$CH_3OC_6H_4$	75	124-126	126-128	C	70.05 (70.95)	4.32 (4.37)

Contd. Table VII.1

1	2	3	4	5	6	7	8	9	10
d	Br	C_6H_5	4-Cl.C_6H_4	72	115-116	114-116	B	67.15 (67.09)	3.65 (3.56)
e	Br	C_6H_5	3,4-$O_2CH_2C_6H_3$	74	131-133	132-134	A	68.56 (68.49)	3.80 (3.72)
f	Br	4-$CH_3C_6H_4$	C_6H_5	78	118-120	120-122	C	74.65 (74.59)	3.85 (3.78)
g	Br	4-$CH_3C_6H_4$	4-$CH_3OC_6H_4$	64	98-100	96-98	B	71.40 (71.46)	4.73 (4.71)
6h	Br	4-ClC_6H_4	4-$NO_2C_6H_4$	62	190-192	189-191	C	62.23 (62.27)	2.85 (2.81)
i	Br	2-$C_{10}H_7$	C_6H_5	59	172-174	174-176	A	76.29 (76.28)	4.14 (4.16)
j	Br	2-$C_{10}H_7$	4Cl.C_6H_4	70	175-177	176-178	B	70.38 (70.35)	3.58 (3.61)
k	Br	1-$C_{10}H_7$	3-$CH_3C_6H_4$	62	192-194	191-193	B	76.58 (76.60)	4.48 (4.49)

Contd. Table VII.1

1	2	3	4	5	6	7	8	9	10
l	Br	4-$C_6H_5C_6H_4$	C_6H_5	60	161-163	162-164	A	77.20 (77.24)	4.38 (4.36)
m	Br	2-C_4H_3S	4-$CH_3OC_6H_4$	64	172-174	174-176	C	55.54 (55.58)	3.25 (3.26)
7a	NO_2	C_6H_5	C_6H_5	45	91-93	94	A	81.14	4.63
b	NO_2	C_6H_5	4-$CH_3C_6H_4$	48	110-112	112	B	81.91 (81.89)	5.03 (5.01)
c	NO_2	C_6H_5	4-$CH_3OC_6H_4$	42	132-134	128-130	C	77.58 (77.74)	4.73 (4.78)
d	NO_2	C_6H_5	4-ClC_6H_4	50	111-113	115	B	73.90 (73.99)	3.82 (3.89)
e	NO_2	C_6H_5	3-,4-$O_2CH_2C_6H_3$	45	132-134	133	A	74.75 (74.80)	4.10 (4.06)
f	NO_2	4-$CH_3C_6H_4$	C_6H_5	35	120-122	118-120	B	81.35 (81.41)	5.04 (5.01)
g	NO_2	4-$CH_3C_6H_4$	4-$CH_3OC_6H_4$	45	94-96	96	A	78.12 (78.10)	5.16 (5.14)

Contd. Table VII.1

1	2	3	4	5	6	7	8	9	10
h	NO_2	4-Cl.C_6H_5	4-$NO_2C_6H_4$	48	190-191	1888	B	66.14	3.27
								(66.0)	(3.25)
i	NO_2	2-C_{10}-H_7	C_6H_5	38	173	171-172	A	83.30	4.61
								(83.20)	(4.55)
j	NO_2	2-$C_{10}H_7$	4-ClC_6H_4	52	176-177	178	B	76.14	3.92
								(76.19)	(3.90)
k	NO_2	1-$C_{10}H_7$	3-$CH_3C_6H_5$	32	189-191	192-194	C	82.63	5.27
								(82.53)	(5.29)
l	NO_2	4-$C_6H_5C_6H_4$	C_6H_5	47	164-166	165	B	83.70	4.76
								(83.79)	(4.73)
m	NO_2	2-C_4H_3S	4-$CH_3OC_6H_4$	50	176-178	177	C	77.03	5.04
								(79.74)	(5.06)

A = Benzene: pet ether, B = Chloroform : pet Ether C = Benzene : Chloroform:

Table VII.2 – IR Data (KBr) cm^{-1} of naphthalene (5a-7m)

Compound	IR data (KBr) Cm^{-1}				
	ν C-H	ν C=C	φ C-H	ν $C-NO_2$	νC-X(Cl,Br)
1	2	3	4	5	6
5a	3030	15959	90	—	780
b	3045	15959	95	—	775
c	3080	15989	92	—	785
d	3110	16109	95	—	780
e	3120	16059	92	—	782
f	3075	16059	95	—	788
g	3060	15859	92	—	782
h	3068	19109	95	1505,1335	790
i	3075	1615	990	—	795
j	3090	16129	95	—	798
k	3070	16059	90	—	790
l	3095	16009	92	—	775
m	3100	16059	90	—	780
6a	3045	16109	95	—	695
b	3050	16009	90	—	710
c	3085	16059	85	—	705
d	3095	15959	95	—	720
e	3105	16109	90	—	700
f	3130	16051	005	—	695
g	3085	16159	95	—	685
h	3105	16089	98	1505,1340	695
i	3085	16009	90	—	690
j	3065	15959	95	—	695
k	3095	16101	000	—	700

Contd. VII.2

1	2	3	4	5	6
i	3075	16059	98	—	675
m	3110	16109	95	—	695
7a	3095	16059	92	1500, 1330	—
b	3090	16089	98	1515, 1335	—
c	3100	16159	90	1520,1325	—
d	3070	16059	92	1510,1320	—
e	3090	1595	990	1505, 1310	—
f	3105	16059	95	1505,1340	—
g	3122	16059	92	1500,1340	—
h	3145	16189	88	1510,1325	—
i	3110	16059	96	1515,1335	—
j	3105	16109	92	1525,1335	—
k	3115	16009	82	1505,1310	—
l	3060	15989	90	1500,1325	—
m	3075	16009	95	1505,1330	—

ν = Stretching Vibrations

ϕ = Out of plane deformation of hydrogen attached to aromatic Nucleus

Table VII.3 – NMR ($CDCl_3$) data of napthaline (5a-7m)

Compound	δ (PPm)	No. of Protons	Assignment to Protons
1	2	3	4
5b	2.50,s	3H	CH_3
	6.92-8.22m	14H	Pheny 1+naphty1
c	3.80,s	3H	OCH_3
	6.82-8.24, m	14H	Pheny 1+naphty1
c	6.05,s	2H	$-O_2CH-_2$
	6.72-8.15,m	13H	pheny1+naphthy1
g	3.75,s	3H	OCH_3
	2.35,s	3H	CH3
	6.85-8.06,m	13H	Pheny1+naphthy1
k	2.35,s	3H	CH_3
	6.80-825,m	16H	Pheny1+naphthy1
m	3.80,s	14H	OCH_3
	6.88-8.20,m	12H	Pheny1+naphthy1
6b	2.40,s	3H	CH_3
	6.85-8.25,m	14H	Pheny1+naphthy1
c	3.75,s	3H	OCH_3
	6.75-3.20,m	14H	Pheny1+naphthy1
e	6.00,s	2H	O_2CH_2
	6.65-8.10,m	13H	Pheny1+naphthy1
f	2.40,s	3H	CH_3
	6.75-8.10,m	14H	Pheny1+naphthy1
g	3.70,s	3H	OCH_3
	2.30,s	3H	CH_3
	6.80-8.20,m	13H	Pheny1+naphthy1

Contd. VII.3

1	2	3	4
k	2.45,s	3H	CH_3
	6.80-8.20,m	16H	Phenyl+naphthyl
m	3.70,s	3H	OCH_3
	6.65-8.10,m	12H	Phenyl+naphthyl
7b	2.48,s	3H	CH_3
	6.95-8.30,m	14H	Phenyl+naphtyl
c	3.87,s	3H	OCH_3
	6.87-8.29,m	14H	Phenyl+naphthyl
e	6.03,s	2H	$-O_2CH_2-$
	6.72-8.15,m	13H	Phenyl+naphthyl
f	2.33,s	3H	CH_3
	6.77-8.15,m	14H	Phenyl+naphthyl
g	2.35,s	3H	CH_3
	3.75,s	3H	OCH_3
	5.80-8.21,m	13H	Phenyl+naphthyl
k	2.36,s	3H	CH_3
	6.82-8.30,m	16H	Phenyl+naphthyl
m	3.82,s	3H	OCH_3
	6.84-8.26,m	12H	Phenyl+naphthyl +thiopnenyl

s=singlet, m=multiplet

Chapter-VIII

SYNTHESIS OF SOME NEW 2-ARYLINDOLES AND 2-ARYLBENZINDOLES VIA AZA RINGCLOSURE REACTION OF 4-FLUOROBENZYLIDENEPYRIDINIUM BROMIDE AND 4-FLOUROBENZYLIDENEDIMETHYLSULFONIUM BROMIDE WITH AROMATIC AMINES*

VIII.1 Abstract

4-Fluorophenacylpyridinium bromide and 4-fluorophenacyldimethylsulfonium bromide on refluxing with substituted anilines in presence of dimethylaniline gave 2-arylindoles in 40-70% yields. The reacton of these salts with 1-aminonaphthalene and 2-aminonaphthalene gave 2-arylbenzindoles. The reaction proceeds via the nucleophilic attack of aniline to the carbonyl group of pyridinium and sulfonium salts which, in turn, undergo ylide formation after dehydrohalogenation. The structures of all new indoles were confirmed by elemental, IR and NMR spectral analyses.

VIII.2 Introduction

Sulfonium ylides and their precursors (sulfonium salts) have been utilized as versatile reagents in the syntheses of a large variety

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* A part of this work has been communcinated for publication in J. Ind. Chem. Soc. (2008)

of acyclic, cyclic and heterocyclic systems[1-7]. Noteworthy in this regard, are the syntheses of substituted naphthalenes[1], epoxides[2], aziridines,[3-5] tetrazines[6] and pyridines[7]. These syntheses of various products were carried out with a view to compare the synthetic utility of sulfonium ylides with analogous ylides of other heteroatom of V group elements[8-16]. In several cases sulfonium ylides follow the path of pyridinium ylides[8-11] and arsonium ylides[12-14].

Therefore in continuation to our earlier work, using pyridinium and sulfonium ylides in the synthesis of substituted pyrimidines, substituted naphthalenes and pyridines[17-18], now in present cahpters, I ~~we~~ have extended our studies in utilizing pyridinium and sulfonium ylides in synthesis of indoles and benzindoles derivatives with a view to test the domain of applicability and comparability of these ylides.

VIII.3 Results and Discussion

The reaction of 4-fluorophenacyl bromide with pyridine in diethylether or THF at reflux temperature gave 4-fluorophenacy-lpyridinium bromide (1a). Similarly, 4-fluorophenacyl bromide with dimethylsulfide in acetone at room temprature gave 4-fluorophenacyl-dimethylsulfonium bromide (1b). The structures of these salts (1a-b) were supported on the basis of compatibility of m.p. and spectral data to that reported in literature.[19-20]. (Scheme VIII.1)

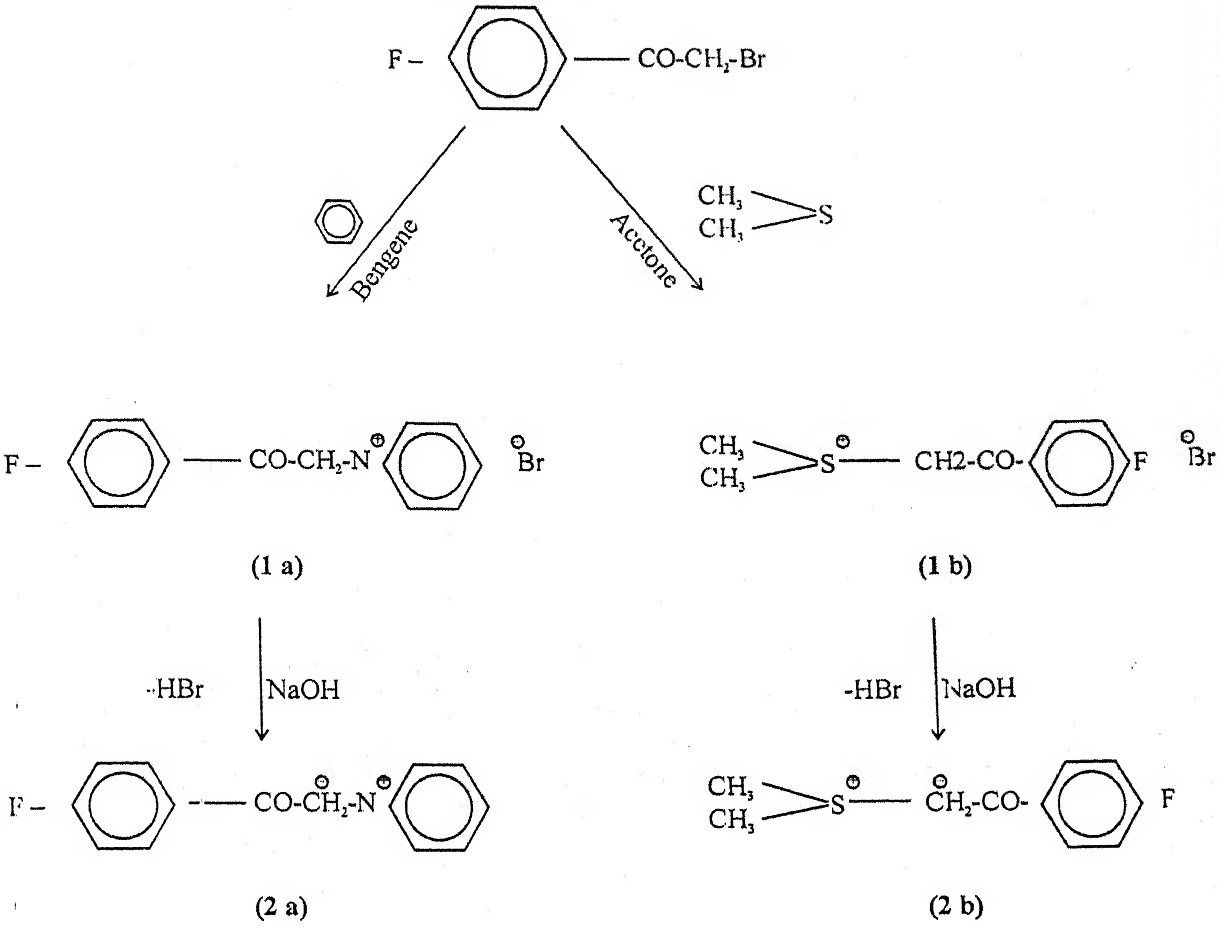
These salts (1a-b) on treatment with aqueous NaOH or K_2CO_3

generated a yellow colouration of 4-flourophenacyipridiniumylide (2a) and 4- flourophenacylidenedimethyl sulfonium ylide (2b). The reaction of pyridinium salt (1a) (route A) or sulfonium salt (1b) (route B) with substituted anilines (3) in dimethylaniline at reflux temperature gave the same 2-(4-fluorophenyl indoles (4a-r) in 45-60% yields (by route A) and 55-70% yields (by route B). (Scheme VIII.2). Similarly, the reaction of 1-naphthylamine (5a) with 1a as well as with 1b in dimethylaniline gave 2-(4-fluorophenyl) benz (g) indoles (6) in 55% and 60% yields respectively. (Scheme VIII.3). The reaction of 1a or 1b with 2-naphthylamine (5b) carried out in dimethylaniline at reflux temperature afforded 2-(4-fluorophenyl) benz (e) indole (7) in 50% and 75% yields respectively. (Scheme VIII.4).

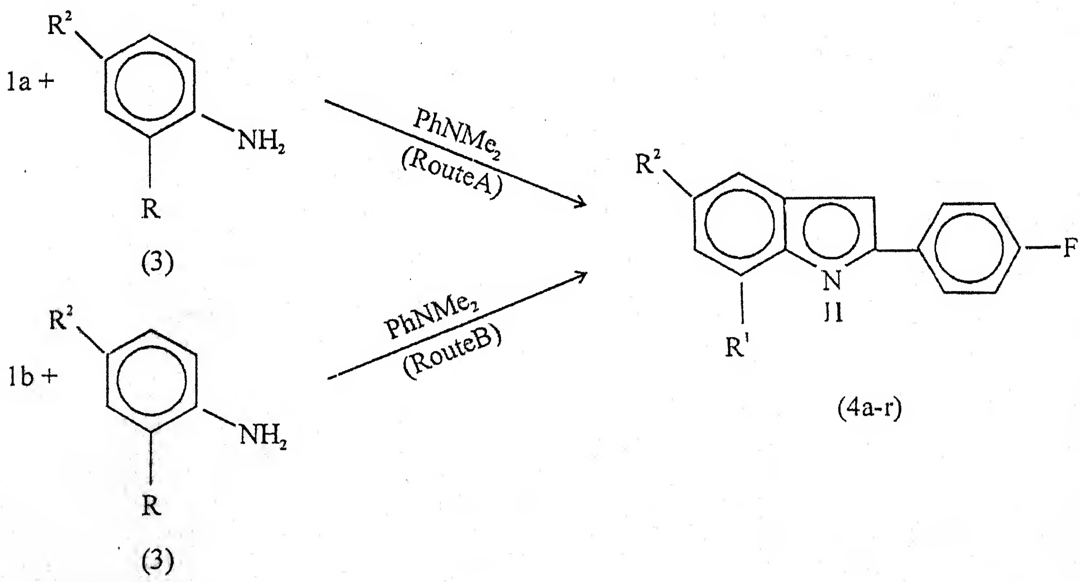
The reaction can also be carried out using triethylamine in place of dimethylaniline, but the yield of the product was lower in this case. The reaction of sulfonium salt (1b) afforded better yields than the one gives by the pyridinium salt (1a).

The plausible mechanism of sulfonium salts (1b) with various anilines (3) was parallelled to the analogous to pyridinium salt (1a)[8-11]. Another possible route for the formation of indoles could be via the initial conversion of the pyridinium bromides (1a) and sulfonium bromide (1b) into corresponding ylides (2a-b). The ylides (2a-b) further reacted with anilines (3) and naphthylamines (5a-b) to give indole derivatives as reported by Junjappa[16]. But the possibility was,

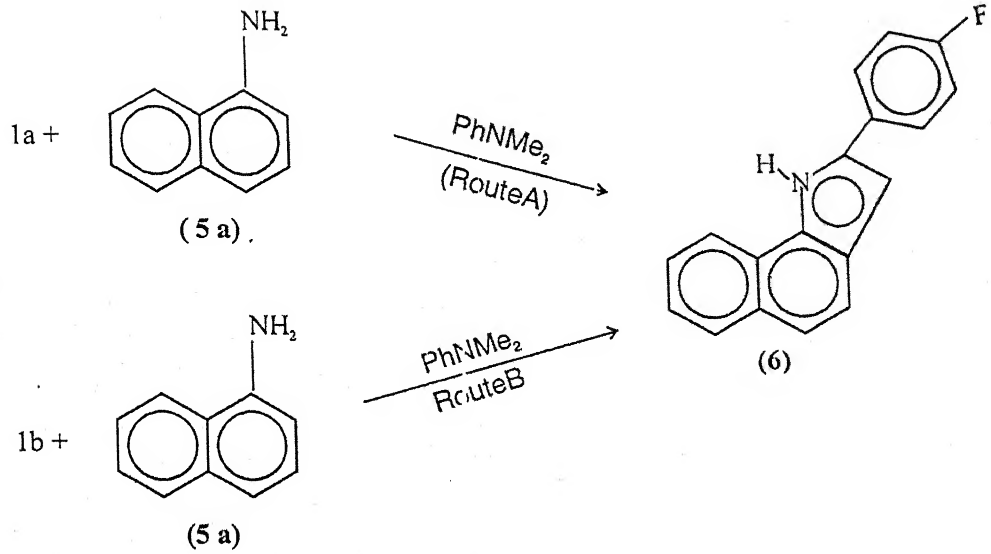
Scheme -1



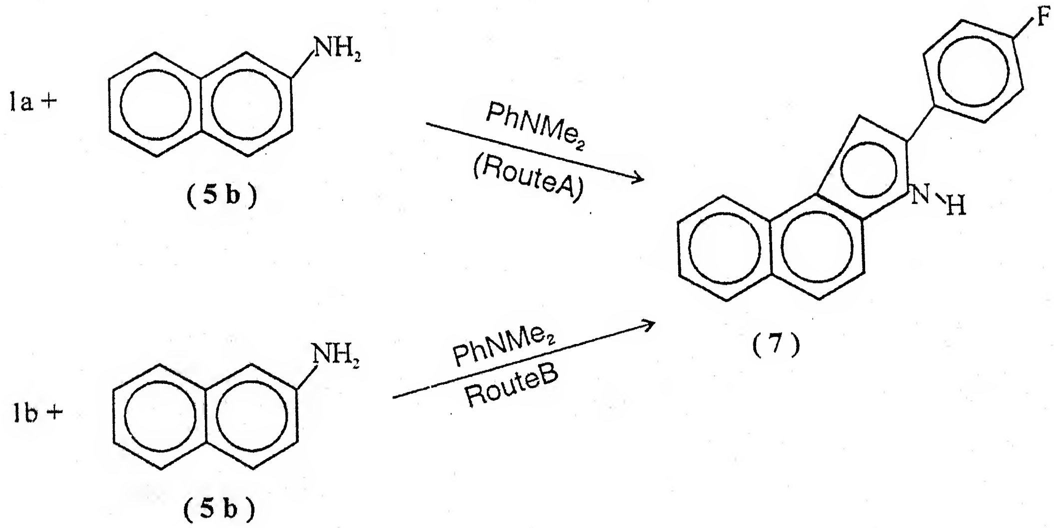
Scheme -2



Scheme -3



Scheme -4

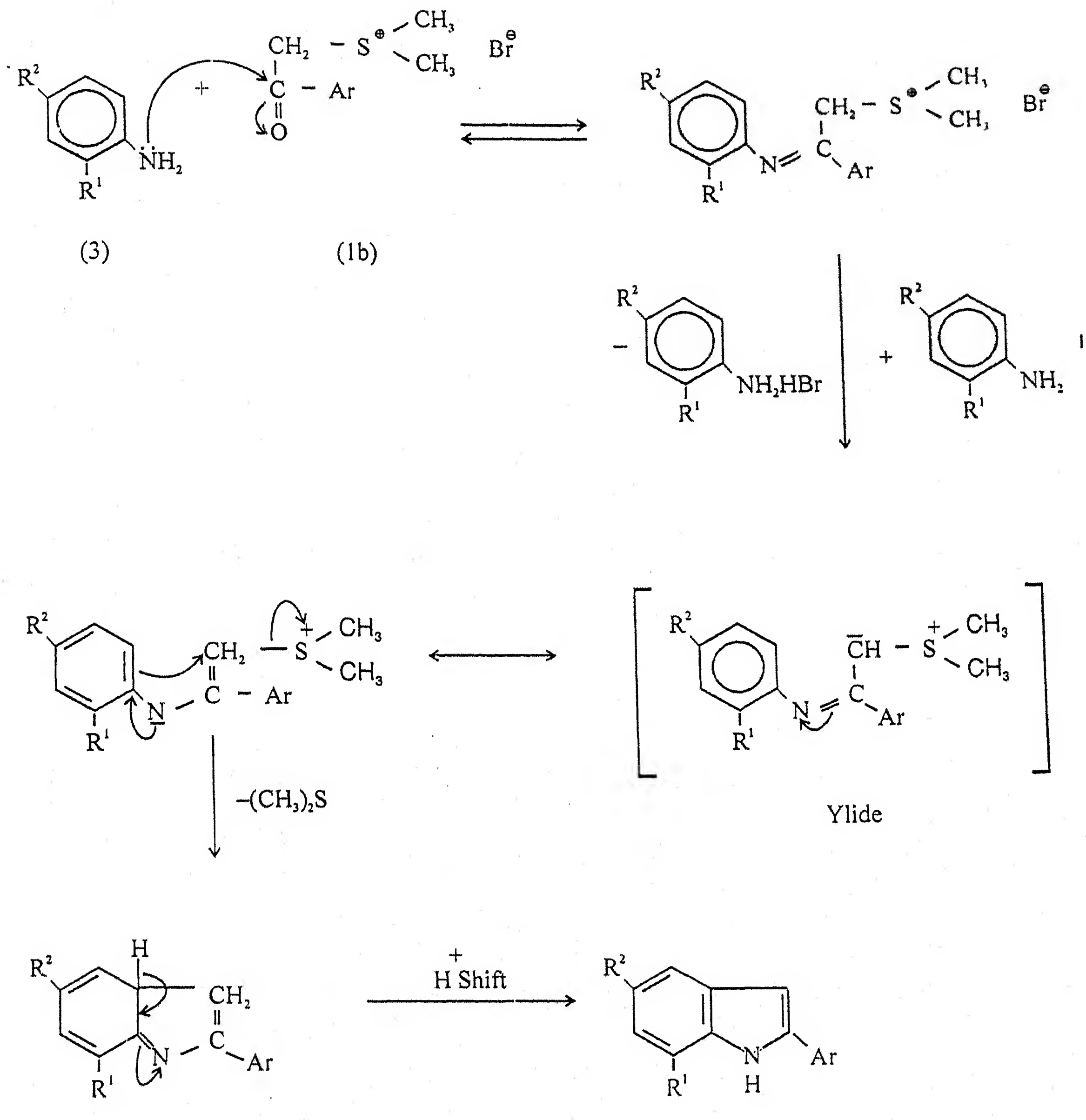


however, discarded in view of the fact that the enhanced stability of ylides (2a-b) resulting from delocalization of (-)ve charge on to carbonyl oxygen was, expected to diminish its reactivity towards anilines. This was further supported that indole derivatives could be only obtained by the ylides when anilinehydrobromide was used. The ylide being a stronger base than aniline, would also react with anilinium bromide to form aniline and corresponding pyridinium and sufonium salts (1a-b). The salts subsequently was attacked on its carbonyl group by the nucleophilic aniline.

The couse of reaction intially involved the nucleophilic attack of aniline (3) on the carbonyl group of salt (1a-b) to form pyridinium or sulfonium salt which underwent ylide formation with aniline base. The ylide thus formed, attacked on free α position of aniline (3) to form indole derivatives with the eliminition of Me_2S. Later, in turn, underwent H shift to form 2-arylindoles. (Scheme VIII. 5)

All the new indoles (4a-r) synthesized were estabilished on the basis of elemental analysis, IR and NMR spectral data. The IR (KBr) spectral data showed a sharp peak in the region 3450-3380 which is attributed to N-H stretching vibration (Table VIII 2). In NMR ($CDCl_3$) spectral data, a broad unresolved peak or a pair of doublet was observed in the region d 7.75-8.25 which corresponded to N-H proton singlet, centered at δ6.40-6.95 was assigned to C_3-H. The aromatic protons were observed in the region δ6.80-7.90 an multiplet (Table

Scheme -5



(4a – r)

(Ar = 4–F-C_6H_4-)

VIII 2)

VII. 4 Experimental

Starting Material

All the reagents obtained from commercial source (E Merk, BDH, SISCO etc). The pyridium salt (1a) and sulfonium salt (1b) were prepared from reaction of 4-fluorophenacyl bromide with pyridine and dimethylsulfide according to the procedure reported in literature[19-20].

General procedure of prepartion 2-arylindoles (4a-r) & 2-arylbanzindoles (6&7)

Route A

A mixture of salt (1a) (10mmol) and subsitituted anilines (30mmol) (3 & 5) was refluxed in 50ml of N, N-dimethylaniline for 6 - 8 hrs. The mixture was cooled and neutrallized with 10% HCl and extracted with dry ether. The ether extract washed with water, dried over anhyd. Na_2SO_4 and evaporated to give crude product which was chromatographed using Al_2O_3 as adsorbent and benzene : pet. ether (1:1) as eluent. The product on recrystallized from suitable solvent gave titled indoles (4a-r, 6,7) shown in the table VIII.1.

Route B

The solution containing 10mmol of salt (1b) and 30mmol of subsitituted aniline (3&5) in 100 ml of N, N-dimethylaniline, was reflexed for 4-6 hrs. The mixture after cooling was neutrallized with 10% HCl and extracted with solvent ether. The dried extract on

evaporation gave crude product which was chromatographed using Al_2O_3 as adsorbent and benzene : pet. ether (1:1) as eluent. The product on recrystallized from suitable solvent gave titled indoles (4a-r, 6,7) shown in the table VIII.1.

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Table 1 : Physical Properties of 2-arylindoles (4a-r) and 2 arylbenzindoles (6 & 7)

Comp-ound	R1	R2	Yield%	Raute	m.p.°c	Anal data Found (Caled) %		
						C	H	N
1	2	3	4	5	6	7	8	9
4a	H	H	60[a]	A	188-90	79.68(79.62)	4.82(4.74)	6.30(6.22)
	H	H	65[a]	B	190-92	79.72 (79.62)	4.80 (4.74)	6.26(6.22)
b	CH_3	H	58[b]	A	170-72	80.12 (80.00)	5.38 (5.33)	6.30 (6.22)
	CH_3	H	60[b]	B	171-73	80.20 (80.00)	6.36 (5.33)	6.32 (6.22)
c	CH_3O	H	50[a]	A	180-82	74.73 (74.69)	4.90 (4.98)	5.96 (5.81)
	CH_3O	H	58[a]	B	178-80	74.70 (74.69)	4.92 (4.98)	5.9 (5.81)
d	Cl	H	55[c]	A	130-32	68.48 (68.42)	3.69 (3.67)	5.76 (5.70)
	Cl	H	60[c]	B	131-33	68.36 (68.43)	3.60 (3.67)	5.77 (5.70)
e	Br	H	50[d]	A	125-27	59.98 (59.93)	3.15 (3.10)	4.80 (4.83)
	Br	H	55[d]	B	124-26	59.86 (59.93)	3.04 (3.10)	4.80 (4.83)
f	I	H	50[b]	A	130-32	49.90 (49.85)	2.60 (2.67)	4.25 (4.15)
	I	H	60[b]	B	128-30	49.90 (49.85)	2.43 (2.67)	4.20 (4.15)

Contd. Table VIII.1

1	2	3	4	5	6	7	8	9
g	F	H	55[a]	A	145-46	73.46 (73.36)	3.82 (3.93)	6.17 (6.11)
	F	H	58[a]	B	146-48	73.40 (73.36)	3.85 (3.93)	6.22 (6.11)
h	NO_2	H	45[b]	A	102-04	65.70 (65.62)	3.60 (3.51)	10.81(10.94)
	NO_2	H	50[b]	B	100-02	65.68 (65.62)	3.56 (3.51)	10.86(10.94)
i	CH_3	NO_2	40[b]	A	110-12	66.72 (66.65)	4.41 (4.07)	10.47(10.37)
	CH_3	NO_2	45[d]	B	108-10	66.76 (66.66)	4.13 (4.07)	10.43(10.37)
j	CH_3	CH_3	45[d]	A	178-80	80.42 (80.33)	6.19(6.11)	6.15 (6.11)
	CH_3	CH_3	52[d]	B	176-78	80.40 (80.33)	6.14 (6.11)	6.18 (6.11)
k	H	CH_3	50[c]	A	200-202	8.15 (80.00)	5.30 (5.33)	6.28 (6.22)
	H	CH_3	55[c]	B	202-204	80.10 (80.00)	5.40 (5.33)	6.32 (6.22)
I	H	OCH_3	45[d]	A	196-98	74.76 (74.69)	4.90 (4.98)	5.94 (5.81)
	H	OCH_3	50[d]	B	198-200	74.60 (74.69)	4.94 (4.98)	5.88 (5.81)
m	H	Cl	60[a]	A	172-74	68.52 (68.43)	3.60 (3.67)	5.78 (5.70)
	H	Cl	65[a]	B	175-77	68.55 (68.43)	3.72 (3.67)	5.65 (5.70)

Contd. Table VIII.1

1	2	3	4	5	6	7	8	9
n	H	Br	55^{c}	A	186-88	59.85 (59.93)	7.16 (3.10)	4.95 (4.83)
	H	Br	62^{c}	B	184-86	59.86 (59.93)	3.14 (3.10)	4.89 (4.83)
o	H	I	40^{b}	A	170-72	49.72 (49.85)	2.61 (2.67)	4.22 (4.15)
	H	I	50^{b}	B	174-75	49.78	2.72	4.52
p	H	I	58^{c}	A	180-82	73.48(73.36)	3.86 (3.93)	6.20(6.11)
	H	I	62^{c}	B	184-83	73.30 (73.36)	3.98 (3.93)	6.15 (6.11)
q	H	NO_2	45^{d}	A	162-64	65.71 (65.62)	3.43 (3.51)	10.86(10.94)
	H	NO_2	50^{d}	B	163-65	55.76(65.62)	3.43(3.51)	10.88(10.94)
r	NO_2	CH_3	48^{d}	A	130-32	66.72(66.66)	4.15(4.07)	10.43(10.37)
	NO_2	CH_3	55^{d}	B	128-29	66.78(66.66)	4.11(4.07)	10.32(10.37)
6	--	--	55^{b}	A	208-10	82-85(82.76)	4.52(4.59)	5.31(5.36)
	--	--	60^{b}	B	211-130	82.70 (82.76)	4.55 (4.59)	5.41(5.36)
7	--	--	50^{c}	A	210-12	82.66 (82.76)	4.53 (4.59)	5.43 (5.36)
	--	--	55^{c}	B	206-08	82.70 (82.76)	4.52 (4.59)	5.40 (5.36)

Recrystn Solvents : a = C_6H_6-$CHCl_3$; b = C_6H_6-CH_3COCH_3 c = $CHCl_3$-CH_3OH d = C_6H_6-CH_3OH

Table VIII. 2. Spectral data of 2 arylindoles (4a-r) and 2 arylbenzindoles (6&7)

Compound	NMR ($CDCl_3$) data δ(ppm)	No of H	Assignment	IR (KBr) data cm^{-1} γc-H	νC-C	φc-H	νN-H
1	2	3	4	5	6	7	8
4a.	7.85,b	1H	N-H	3150	1610	990	3390
	6.50,d	1H	C_3-H				
	6.85-7.60, m	8H	Ar-H				
b.	7.75,d	1H	N-H	3120	1615	985	3380
	6.40,d	1H	CH				
	2.45,s	3H	CH_3				
	6.80-7.50,m	7H	ArH				
c.	8.06,b	1H	N-H	3145	1625	998	3410
	6.75,d	1H	C_3H				
	3.85,s	3H	OCH_3				
	6.75-7.60,m	7H	ArH				
d.	8.15,b	1H	N-H	3150	1620	995	3415
	6.80,b	1H	C_3-H				
	7.50-7.85,m	7H	ArH				
e.	8.10,b	1H	NH	3155	1605	988	3390
	6.75,d	1H	C_3-H				
	7.90-7.80,m	7H	ArH				
f.	8.00,b	1H	N-H	3140	1615	995	3405
	6.70	1H	C_3-H				
	7.90-7.80,m	7H	ArH				
h.	8.35,b	1H	N-H	3165	1610	990	3420
	6.95,d	1H	C_3-H				
	7.00-7.80,m	7H	ArH				

1	2	3	4	5	6	7	8
i	7.85,m	1H	N-H	3150	1618	998	3415
	6.50,d	1H	C_3H				
	2.50,d	1H	CH_3				
	6.80-7.70, m	6H	ArH				
j	7.80,b	1H	N-H	3125	1605	995	3405
	6.55,d	1H	C_3-H				
	2.40,s	3H	CH_3				
	2.50,s	3H	CH_3				
	6.65-7.50, m	6H	ArH				
k.	7.85,b	1H	N-H	3125	1610	988	3390
	6.65,d	1H	C_3-H				
	2.45,s	3H	CH_3				
	6.85-7.60,m	7H	ArH				
I.	7.90,b	1H	N-H	3148	1615	995	3415
	6.68,d	1H	C_3-H				
	3.80,s	3H	OCH_3				
	6.70-7.55,m	7H	ArH				
m.	8.20,b	1H	N-H	3150	1622	998	3420
	6.85	1H	C_3-H				
	7.00-7.85,m	7H	ArH				
n.	8.12	1H	N-H	3148	1620	995	3415
	6.88	1H	C_3-H				
	7.15-7.90,m	7H	ArH				
o.	8.05	1H	N-H	3135	1610	992	3400
	6.68	1H	C_3-H				
	6.95-7.88,m	7H	ArH				

Contd. Table VIII.2

1	2	3	4	5	6	7	8
p.	8.20,b	1H	N-H	3158	1625	995	3418
	7.50,d	H	C_3-H				
	7.20-8.10, m	7H	ArH				
q.	8.30,b	1H	N-H	3165	1615	998	3425
	6.90,d	1H	C_3-H				
	7.10-790, m	7H	ArH				
r.	7.90,b	1H	N-H	3150	1615	995	3410
	6.65,d	1H	CH				
	2.48,s	3H	CH_3				
	6.90-7.75,m	6H	ArH				
6.	8.30,q	1H	N-H	3140	1615	995	3430
	6.70,d	1H	C_3-H				
	6.85-8.10,m	10H	ArH				
7.	7.15,q	1H	NH	3145	1620	998	3435
	6.60,d	1H	C_3-H				
	6.75-7.95, m	10H	ArH				

s=singlet; b=broad peak; d=doublet; q = quartet m=multiplet

γ=stretching vibrations; ϕ=out of plan deformation of H attached to C=C